Chapter Four

Priority Setting

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I. Introduction

A. Charge to the PSWG

This chapter of the EDSTAC report addresses the need to set priorities for endocrine disruptor screening and testing. It was developed by the Priority Setting Work Group (PSWG) and was reviewed, refined, and endorsed by the EDSTAC. The PSWG consisted of nineteen individuals representing a wide diversity of perspectives and backgrounds including various sectors of industry; a variety of state and federal government agencies; national environmental, worker, and public health-oriented organizations; and local citizen and environmental justice groups. A complete list of work group members is included in Appendix C. References and sources for this chapter can be found in the Literature Cited section at the end of the chapter and in Appendix F.

The charge given to the PSWG was to:

- specify types of information that should be gathered and analyzed to sort and prioritize chemical substances and mixtures for screening and testing;
- develop criteria for evaluating the quality, adequacy, and reliability of the information that will be used in sorting and prioritizing chemical substances and mixtures for screening and testing;
- develop criteria for sorting chemical substances and mixtures into four possible next steps, including: (1) hold screening and testing; (2) prioritize for Tier 1 Screening (T1S); (3) go to Tier 2 Testing (T2T); or (4) go to hazard assessment;
- develop criteria for setting priorities for T1S. These criteria will address the relative order of priority in which chemical substances that are sorted into this category will actually proceed to T1S; and
- suggest how information used for priority setting should be combined with screening and testing results to generate a "weight-of-evidence" determination for proceeding from screening to testing or from testing to hazard assessment.

B. The Need for Priority Setting

Priority setting for endocrine disruptor screening and testing is not a trivial exercise. Industrial chemicals, pesticides, commercial products, and environmental contaminants have been subjected to various screening and testing regimes for decades (Swanson and Socha, 1997). However, the existing regulatory screening and testing schemes do not specifically address endocrine disrupting mechanisms. The chemicals in commerce and the environment exhibit a range of physical and/or chemical and toxicological properties, as well as varied production and use patterns. Only some chemicals are likely to cause endocrine disruption, and only some of these chemicals will be produced or used in such a fashion that humans or other living organisms will be exposed to them. Because screening and testing can be such a resource-intensive process for both the public and private sectors, priorities must be set carefully to ensure that the chemicals of greatest concern are given priority over chemicals of little or no concern.

The challenge is daunting. Building on the information contained in Chapter Two, the EDSTAC recommends the universe of chemicals to at least be considered for endocrine disruptor screening and testing should include:

- all of the approximately 75,500 chemicals currently listed on the TSCA Inventory (James Darr, U.S. EPA, personal communication);
- all of the approximately 900 active ingredients (approximately 500 of which are food-use pesticides which will be prioritized for screening and testing according to the schedule and requirements of the FQPA (see Chapter Four, Section XI, H) and approximately 2,500 inert ingredients that are used to formulate over 20,000 pesticide products (Penny Fenner-Crisp, U.S. EPA, personal communication);
- approximately 8,000 chemicals regulated by the Food and Drug Administration (FDA) including 5,000 ingredients in cosmetics and 3,000 food additives (Bern Schwetz, FDA, personal communication);
- naturally occurring non-steroidal estrogens (NONEs) and other naturally occurring or environmentally degraded chemicals; and
- nutritional supplements, for which a number cannot be estimated because these chemicals are not currently regulated by the FDA or any other agency.

Thus, the number of individual chemical substances that should be considered for endocrine disruptor screening and testing exceeds 87,000. Later in this chapter the EDSTAC presents recommendations for screening and testing "commonly found mixtures" as per the scope of the recommended program set forth in Chapter Three. The EDSTAC recognizes that the evaluation of some of the individual chemical substances, if they are determined to be a priority for screening and testing, will require a cooperative effort among the responsible agencies.

In responding to the challenge, the PSWG grappled with a number of practical considerations:

- What scientific criteria should be used in establishing priorities?
- What information is available with respect to these criteria and how readily can the information be analyzed?
- What are the major gaps in information needed for setting priorities and how can these gaps be filled?
- How should the priority setting system be designed to maximize "transparency" (i.e., public understanding of the rationale underlying the established priorities)?
- Should priorities be governed by existing statutory authorities?
- How might priorities be set, without regard to EPA's statutory authority, to encourage voluntary private sector testing and to ensure compounds of concern are addressed?

The EDSTAC's efforts to develop a coherent, scientifically sound framework for setting screening and testing priorities have required EDSTAC members to carefully review the way in which EPA gathers information about new and existing chemicals. The Committee examined the authority provided to EPA by Congress which guide the Agency's data-gathering efforts, and reviewed the Agency's management of the data available to it. The Committee also reached

beyond EPA in its quest for pertinent information sources to guide priority setting. Data on chemical hazards in the environment are also gathered by the Occupational Safety and Health Administration, the U.S. Department of Agriculture, the Food and Drug Administration, the U.S. Department of the Interior, and other federal and state agencies, as well as parties in the private and academic sectors.

Despite the multitude of data-gathering authorities and databases on chemicals, information on exposure to, and the health and environmental effects of, most chemicals is incomplete, and inadequate with respect to endocrine disrupting effects. For example, much more information is available on the effects of pesticides regulated under FIFRA than is available on the effects of industrial chemicals addressed under TSCA. The EDSTAC's priority setting scheme attempts to address these information disparities.

The priority scheme recommended in this chapter reflects an integrated, scientifically driven concern for chemical exposures and effects that transcends the barriers that exist under current federal law. The priority setting scheme described in this chapter is noteworthy in several respects, including:

- First, even though the immediate impetus for endocrine screening and testing lies in provisions contained in the FQPA and the amendments to the SDWA, as described further below, the EDSTAC has not limited its priority setting scheme to chemicals addressed only under the endocrine disruptor screening and testing provisions contained in those two statutes.
- Second, as described in the Conceptual Framework contained in Chapter Three, the EDSTAC has not limited its attention solely to the estrogen mimics that are explicitly mentioned in the FQPA and the SDWA, but is recommending that the initial screening and testing program also include androgen- and thyroid-related hormones. The Committee also recommends periodic review of the initial program to evaluate whether the inclusion of additional hormonal systems is warranted in the future.
- Third, even though the FQPA and the SDWA focus on human health, the EDSTAC decided early in its deliberations that the Endocrine Disruptor Screening and Testing Program (EDSTP) should address environmental impacts as well.
- Fourth, the EDSTAC recommends that the EDSTP should address chemical mixtures in addition to single chemicals.
- Fifth, the priority setting scheme, by promoting the use of robotic screening technologies (referred to as High Throughput Pre-Screening, or HTPS), is designed both to generate new information about chemicals and to help validate chemical modeling techniques that are used to judge hazards in the absence of empirical data.
- Sixth, the Committee deliberately included so-called NONEs (e.g., phytoestrogens, mycotoxins) – substances that naturally occur in the environment – in its priority setting scheme.

It is important to note that the following discussion of the EDSTAC's recommended priority setting scheme does not reflect any interpretation by the EDSTAC of EPA's authority to implement these recommendations. The EDSTAC's priority setting scheme is driven by an overarching concern with exposures to and effects from chemicals. The Committee

acknowledges that EPA's screening and testing actions will be both heavily driven and constrained by its statutory authority.

II. Overview of the Sorting and Priority Setting Recommendations

A. Initial Sorting Step

As described in Chapter Three and graphically depicted in Figure 4.1, the EDSTAC Conceptual Framework consists of three major components: (1) the sorting and priority setting component; (2) the T1S component; and (3) the T2T component. Within the sorting and priority setting component, the EDSTAC has made a distinction between the tasks of "sorting" and of "priority setting."

The term "sorting" is used to refer to the initial effort to sort the universe of chemicals that will be considered for endocrine disruptor screening and testing into four distinct categories. Coming out of the "initial sorting" box, the four possibilities include:

1. polymers which will be placed into a "hold" status (with some exceptions) pending a review of their monomers, oligomers, and other components;
2. chemicals for which insufficient data exist to proceed to either T2T or hazard assessment and will, therefore, need to be prioritized for T1S;
3. chemicals for which sufficient data exist to go to T2T; and
4. chemicals for which sufficient data exist to go to hazard assessment.

The term "priority setting" refers primarily to the need to set priorities for the chemicals that fall into the second category after the initial sorting stage – namely, those chemicals for which insufficient data exist to proceed to either T2T or hazard assessment and will, therefore, need to be prioritized for T1S.

The remainder of this section provides an explanation of the phased approach to screening and testing, a brief overview of each of the four categories of chemicals that flow from the initial sorting step (referred to above), and some of the other key features of the priority setting system recommended by the EDSTAC. The rest of the chapter builds upon this overview section.

B. Phased Approach

The EDSTAC agreed that the EDSTP should be implemented in a phased manner. In general, this means the chemicals determined to be a high priority should be screened and, if necessary, tested prior to those determined to be a lower priority. Two of the reasons for this general agreement on the use of a phased approach to implementation are: (1) to ensure that the program does not get bogged down by taking on too much too fast, both in terms of laboratory capacity and the administrative challenges with implementing a program of this magnitude; and (2) to ensure that periodic programmatic-level evaluations occur that includes the incorporation of new scientific findings, new screens and/or tests, etc. However, the EDSTAC did not have a sufficient amount of information nor the time to develop more refined recommendations about precisely how many phases there should be, how long each phase should be, or the number of chemicals that should be screened and/or tested in each phase. The EDSTAC understands that some of these issues will be addressed by EPA when it issues its detailed implementation plan after the conclusion of the EDSTAC.

Given the elements of the screening and testing program upon which EDSTAC was able to agree, it is clear there are a number of activities which will need to occur immediately following the conclusion of the EDSTAC process and prior to the actual screening and testing of compounds. These activities include the validation and standardization of the recommended T1S assays and Tier 2 tests, the completion of the HTPS assays (assuming they are shown to be technically feasible and are validated), and the completion of the T1S priority setting process. Therefore, if "Phase I" of the program is defined as the start of the actual screening and testing of chemicals, its start date is dependent upon the completion of these preliminary activities. EPA and some industry representatives have indicated that they may wish to make use of a screening assay or test as soon as it is validated, rather than waiting for all screens and tests to be validated. Thus, the start of Phase I may be staggered depending upon the results and timing of the validation process.

During "Phase I" of the program (as defined in the preceding paragraph) T1S will only include those chemicals determined to be a high priority, and T2T will only include those chemicals that bypass T1S. During the second phase of the program, those chemicals that were determined to be positive in T1S will move into T2T, and a new set of priority chemicals will then be subjected to T1S.

Finally, as noted above, one of the reasons for recommending a phased approach to implementation is to ensure that EPA conducts periodic programmatic-level evaluations of the EDSTP. The EDSTAC has stated in several places in this report that the design of the EDSTP needs to be flexible to account for the newly emerging and rapidly evolving scientific investigation of endocrine disruptors. Although the EDSTAC's recommendations regarding flexibility are meant to imply that new scientific findings and new screens and/or tests should be incorporated into the program as they emerge, the EDSTAC believes it is critically important to include an explicit evaluation step into the program. The use of a phased approach to implementation can help to ensure that such evaluations occur. Some of the issues that should be evaluated at the

conclusion of one phase and prior to the start of another relate to the criteria for chemicals coming back into the program when they are placed in the "hold box." These include an evaluation of whether new screens and tests have been developed for the EAT hormonal systems, including, for example, *in utero*/developmental assays and whether new screens and tests have been developed for other hormonal systems.

C. Polymers

In an effort to grapple with the very large number of chemicals that the PSWG had identified as candidates for endocrine disruptor screening and testing, the group spent considerable time addressing the question of which, if any, chemicals should be placed in the "hold box" as part of the initial sorting step. It was thought that a class, or classes, of chemicals with a very low probability of being endocrine disruptors for the hormonal systems addressed by the screening and testing program could be set aside so as to avoid "clogging up" the system.

The group initially identified polymers as one type of chemical that warranted consideration for exclusion because of their molecular size. It was initially thought that polymers would not pose a threat to the endocrine systems of humans and other biota. Subsequently, the group learned there are instances where polymers could be absorbed, particularly in neonates.

Consequently, the EDSTAC recommends that:

1. All monomer and oligomer components of polymers should be prioritized for and subjected to endocrine disruptor screening and testing.

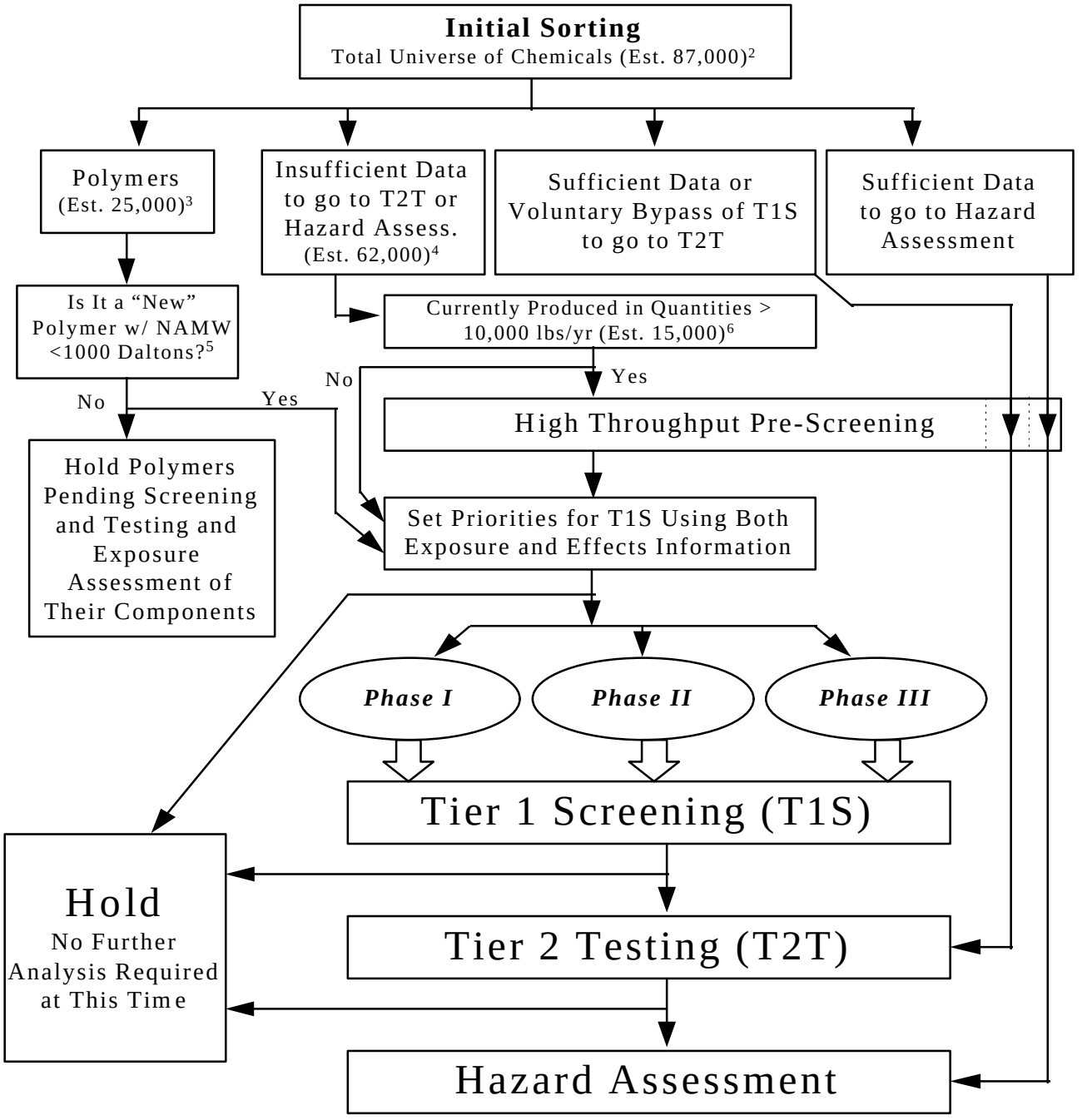
2. All "new" polymers (i.e., those produced after the Initial TSCA Inventory, which was published in 1979) with number average molecular weight (NAMW) less than 1,000 daltons should also be prioritized for and subjected to endocrine disruptor screening and testing. Throughout this document, the term "number average molecular weight," or "NAMW" of polymers is utilized. This term indicates a numerical mean, with the actual MW of the polymers ranging about this mean. The EDSTAC recommends embracing the language in the 1995 Final TSCA Polymer Rule (60 FR 16333) which uses a NAMW cutoff of 1,000 daltons, provided that the polymer does not contain other than certain specified reactive functional groups and that the polymer contains less than 10% oligomers with MW less than 500 daltons and less than 25% oligomers with a MW of less than 1,000 daltons.

3. All previously manufactured polymers (regardless of NAMW) and all "new" polymers with a NAMW greater than 1,000 daltons should be set aside pending the outcome of the screening and testing of their monomer and oligomer and other components.

4. If the component is determined to have endocrine disrupting properties, the component should proceed to hazard assessment.

Figure 4.1

Detailed Depiction of EDSTAC Conceptual Framework[1]



[1] This flow chart represents a more detailed description of the sorting and priority setting components, and how they relate to the Tier 1 Screening (T1S), Tier 2 Testing (T2T), and Hazard Assessment components.
[2] See Chapter Four, Section I. B.
[3] See Chapter Four, Section VI. A. 2.
[4] See Chapter Four, Section II. K. Essentially, this number results from subtracting 25,000 polymers from the total universe of 86,000 chemicals.
[5] See Chapter Four, Section VI. A. 1.
[6] See Chapter Four, Section V. F.

5. As with any chemical shown to have endocrine disrupting properties, an exposure assessment should be performed. It is at this stage, that all potential exposure routes for a component would be determined, including the potential for the component to be available from the polymer. Implications with respect to the polymer itself would be dependent upon the results of such an exposure assessment.

As indicated in Figure 4.1, if this approach is utilized it will place approximately 25,000 polymers of the approximately 87,000 chemicals being considered for endocrine disruptor screening and testing into a "hold box" pending a review of their monomers and oligomers (James Darr, U.S. EPA, personal communication). The rationale for these recommendations, as well as the recommendations themselves, are elaborated upon in Section VI of this chapter.

D. Chemicals With Sufficient Data to go to T2T or Voluntary Bypass of T1S

As noted in Chapter Three, there are two scenarios in which the EDSTAC recommends the owner of a chemical should be permitted to voluntarily bypass T1S. Each of these two scenarios has different implications for the information requirements associated with completing T2T.

1. Chemicals That Have Previously Been Subjected to Two-Generation Reproductive Toxicity Tests

The first scenario includes those chemicals that have previously been subjected to mammalian and wildlife developmental and/or reproductive toxicity testing, but where such testing may not have included additional endpoints for T2T, as specified in Chapter Five, Section V, C. The EDSTAC expects that food-use pesticides will fall into this category, given the requirements of FIFRA, as will a small number of other types of pesticides and industrial chemicals. The EDSTAC agrees that chemicals that meet this criterion for bypassing T1S would still be subjected to the assays that will be part of the HTPS, for the reasons outlined in Chapter Four, Section V, G, 2.

In addition, chemicals that meet this criterion will also be the most likely candidates for the alternative approaches for completing T2T, as discussed in Chapter Five, Section VII, C. As described in more detail in Chapter Four, Section XI, H, the recommended approach for setting priorities for T2T of food-use pesticides is basically to follow the schedule for pesticide re-registration and tolerance reassessments for these chemicals, as per the schedule and requirements of the FQPA. Also in Section XI, H, the EDSTAC discusses the need for special treatment of those pesticides that are likely to complete their tolerance reassessments prior to the completion of the validation and standardization of recommended Tier 2 tests.

2. Chemicals for Which There is no Prior Toxicity Testing

The second scenario includes those chemicals for which the owner of the chemical has decided to voluntarily complete T2T without having completed the full T1S battery or any prior two-generation reproductive toxicity testing. The EDSTAC recommends that these chemicals must also be evaluated in the HTPS assays. In addition, chemicals that bypass T1S under this second scenario must be evaluated in all the tests of the T2T battery (i.e., the mammalian and non-mammalian multi-generation tests with all the recommended endpoints), consistent with the principles governing T2T, which are set forth in Chapter Five, Section V, C. Finally, as discussed in Section XI, H of this chapter, these chemicals should retain their T1S priority ranking for T2T even though they will voluntarily bypass the screening tier. In other words, if these chemicals are deemed to be a high priority for T1S and the owner of the chemical decides to voluntarily bypass T1S, they should also be a high priority for T2T.

E. Chemicals With Sufficient Data to Proceed to Hazard Assessment

The EDSTAC recommends that chemicals for which there are sufficient data to conduct a hazard assessment should be permitted to bypass both T1S and T2T and proceed directly to the hazard assessment step of the process. This option should be available for chemicals that have sufficient data to make either a definitive positive or negative determination that the chemical either does or does not have endocrine disrupting properties for the estrogen, androgen, and thyroid hormonal systems addressed by the program.

This step in the process will require a case-specific review and determination that the same type and quality of information exist for the chemical as would be necessary to move from T2T to hazard assessment. The owner of such a chemical (i.e., the company or companies that produced the chemical) or EPA in the case of an “orphan” chemical (i.e., one that has no owner) would need to show that the screens and tests conducted yielded data that are the “functional equivalent” of data that would have been produced from T1S and T2T. Such functional equivalency will certainly include sufficient dose-response relationship clarification before proceeding to the hazard assessment phase.

The EDSTAC believes that only a small number of chemicals will meet this criterion; however, it did not attempt to identify these chemicals. Rather, the Committee has appropriately deferred this determination to EPA as part of the implementation of the EDSTP. As noted above, such a determination will need to be made on a case-specific basis. When EPA formally proposes its approach to implementing the EDSTP, the Agency should publish more detailed decision-making criteria, data and reporting requirements, and procedures that should be followed to provide the degree of clarity necessary to implement this recommendation.

F. Chemicals with Insufficient Data to go to T2T or Hazard Assessment

A very large number of chemicals will remain after the initial sorting step has separated out polymers (with some exceptions), food-use pesticides, and any chemicals that have functionally equivalent data to bypass T1S, and the small number of chemicals that will be ready for the hazard assessment step. The EDSTAC estimates the number of chemicals that will fall into this category to be approximately 62,000. The EDSTAC has developed a set of recommendations to guide the T1S priority setting process for these chemicals.

As discussed in more detail below, the EDSTAC recommends an approach to setting priorities for T1S without specifying the precise number of chemicals that should ultimately be subjected to T1S. Building on the discussion of the phased approach to implementing the EDSTP, it should, however, be noted that even though approximately 62,000 chemicals will remain after sorting out polymers and the relatively small number of chemicals that will meet the criteria for bypassing T1S and/or T2T, the EDSTAC does not expect that 62,000 chemicals will be subjected to T1S. (See Chapter Four, Section XI, F)

G. Priority Setting Information Categories and Criteria

When the PSWG began its deliberations, the group sought to address the following questions:

- What information is relevant to the task of priority setting?
- Is this information readily available?
- If so, how easily can the information be accessed?
- What is the quality, variability, and reliability of this information?
- Can the information be used as the basis for criteria to determine priorities for endocrine disruptor screening and testing?

In grappling with these questions, the PSWG established three main categories for organizing information and criteria related to priority setting: exposure-related, effects-related, and statutory criteria. The exposure and effects categories and information are consistent with those in Swanson and Socha, 1997. Under each of these main headings, the group identified a number of subheadings:

1. <u>Exposure-Related Information and Criteria</u>

    a) Biological sampling data
        i. Human
        ii. Other biota
    b) Environmental, occupational, consumer product, and food-related data
        i. Air
        ii. Water (including surface water, groundwater, and drinking water)
        iii. Soil/Sediments
        iv. Consumer products
        v. Food
    c) Environmental releases

d) Production volume
e) Fate and transport data and models

2. Effects-Related Information and Criteria

a) Toxicological laboratory studies and databases
b) Epidemiological and field studies and databases
c) Predictive biological activity or effects models (e.g., SAR, QSAR)
d) Results of high throughput pre-screening

3. Statutory Criteria

a) Pesticides, as per FQPA
b) Chemicals found in sources of drinking water affecting significant populations, as per SDWA
c) Chemicals that may have a cumulative effect with pesticides, as per FQPA

For the exposure and effects criteria, the PSWG identified a significant number of data sources, evaluated the quality and strengths and limitations of these data sources, and determined how to best utilize these data sources to accomplish the task of priority setting. The results of this effort are set forth in Section III for the exposure-related criteria, and in Section IV for the effects-related criteria. Appendix G includes a series of detailed matrices containing a list and preliminary evaluation of data sources organized under the exposure and effects subheadings.

H. Role of the Statutory Criteria

The PSWG of the EDSTAC discussed the proper role of the statutory criteria listed above in relation to the other criteria. The EDSTAC understands that the screening and testing requirement for pesticides (both active and "inert" ingredients) contained in the FQPA is mandatory. However, the EDSTAC also understands the screening and testing of chemicals found in sources of drinking water affecting significant populations under the SDWA and chemicals that may have a cumulative effect with pesticides under the FQPA to be discretionary.

While recognizing the importance of the statutory criteria in relation to EPA's implementation authorities, the Committee has developed its priority setting recommendations based on public health and environmental concerns rather than on existing regulatory requirements. Thus, the Committee recommends that the statutory criteria should not be used as a sole basis for establishing priorities for endocrine disruptor screening and testing. The Committee recognizes that this recommendation might result in a chemical substance or mixture being identified as a high priority for endocrine disruptor screening and testing for which EPA does not have authority to require such screening and testing under FQPA. Nevertheless, the Committee believes it is important to have priorities driven by scientific considerations and explicit value judgments, rather than by existing regulatory requirements.

The Committee is hopeful that when a chemical is identified as a high priority for T1S that falls outside the scope of the FQPA and the SDWA, the owner of the chemical would voluntarily conduct T1S and, if necessary, T2T. The Committee acknowledges, however, that reliance on authority other than FQPA may affect the timing of actually conducting T1S, notwithstanding the priority ranking of the chemical.

I. High Throughput Pre-Screening (HTPS) Step

One problem the PSWG identified early on in its deliberations is the lack of endocrine disruptor effects-related data on the vast majority of chemicals and their breakdown products. The PSWG considered recommending the use of published and available Quantitative Structure Activity Relationship (QSAR) models to obtain predictions for the endocrine disrupting potentials of untested compounds. Although promising, available QSAR models are generally thought to be insufficiently validated for the diversity of chemicals that will be included in endocrine disruptor screening and testing (Ankley et al., 1997). Therefore, it was the PSWG's determination that QSARs were currently incapable of providing accurate predictions for this highly diverse universe of chemicals. To rectify this problem, the work group recommended, and the plenary endorsed (subject to a demonstration of feasibility), incorporating into the EDSTAC Conceptual Framework the use of "high throughput pre-screening," or the use of automated processes (robotic and specialized instrumentation) to aid in the screening of compounds (discussed in more detail in Chapter Four, Section V). The feasibility demonstration effort for HTPS is described more fully both in Section V of this chapter and in Appendix I.

The primary purpose of HTPS would be to address the fact that there is very little, if any, biological effects information for humans, and even less for other species, on the vast majority of chemicals to be considered for endocrine disruption screening and testing. The assays that will be conducted during the HTPS step of the process are transcriptional activation assays for the three hormonal systems (estrogen, androgen, and thyroid hormone-related). Two of the HTPS assays (ER and AR binding/transcriptional activation) are part of the T1S battery. Any chemicals subjected to the assays conducted in the HTPS step would not be required to repeat the ER and AR binding/transcriptional activation assays as part of T1S. On the other hand, any chemicals which are subjected to T1S but not to HTPS (e.g., production volumes less than 10,000 pounds per year) would go through the *in vitro* assays on the bench as part of T1S, thereby resulting in information equivalent to that which would have been provided from HTPS.

However, the assays in the HTPS step will be far from comprehensive or definitive. The HTPS assays will certainly provide valuable information on the potential of a chemical to bind to the relevant receptor in cell culture and result in transcriptional activation, which is information that is missing for a large number of chemicals. However, the results of HTPS will *not* be sufficient

by themselves to support the conclusion that a chemical is or is not an endocrine-mediated toxicant.

Data resulting from HTPS will be combined with exposure-related information, and with any other effects-related information that is available, for each chemical for the purpose of setting priorities for T1S. In other words, HTPS data will not be used in isolation of other relevant data, nor will it become the *de facto* determinant of priorities for T1S.

Although the use of robotic technology will greatly expand the "throughput" of chemicals over a given period of time for the selected assays, the EDSTAC does not recommend that all chemicals be subjected to HTPS. Rather, the EDSTAC recommends that the estimated 15,000 chemicals currently produced in an amount equal to or greater than 10,000 pounds per year and all pesticides be subjected to HTPS. The EDSTAC makes this recommendation to help EPA avoid a task that might never be completed if a higher number of chemicals were to be recommended for HTPS. Also, the EDSTAC believes that 15,000 chemicals is not an insignificant number of chemicals, especially given the history of TSCA.

The EDSTAC further recommends that chemicals permitted to bypass T1S and go directly to T2T, as well as those permitted to bypass both T1S and T2T and go directly to hazard assessment due to functional equivalency of data, also be subjected to HTPS. There are several generic reasons why the EDSTAC recommends conducting HTPS assays on these chemicals which include: (1) the data generated from the HTPS assays will be valuable in and of themselves, even though they are limited to receptor-binding mechanisms and cannot be used by themselves to determine whether a chemical is or is not an endocrine disruptor; (2) as an ancillary benefit, the data can be used to improve and validate QSARs; and (3) beyond these generic benefits, in the case of food-use pesticides that will complete tolerance reassessments prior to the availability of validated Tier 2 tests, HTPS data can be used along with other relevant information to help prioritize whether and, if so, when these chemicals should be subjected to any additional endocrine disruptor testing. The rationale for recommending that food-use pesticides complete HTPS assays is further elaborated upon in Chapter Four, Section XI, H.

The EDSTAC recommends that existing QSAR models be rederived and supplemented with data from the HTPS assays, thereby expanding the predictive ability of these models. Existing QSARs are derived using data from cell-free receptor binding and cellular proliferation assays. These assays are part of the T1S battery, as specified in Chapter Five, Section III. New QSARs using HTPS data and transcriptional activation potencies from whole cell assays will need to be developed. These new models will likely be expansions of existing QSARs if the same chemical compounds are included in both.

Thus, when it comes time to set priorities for the first phase of T1S, HTPS data (as well as improved QSARs) should be used along with other relevant exposure and effects data. Chemicals not subjected to HTPS (because they are produced in amounts less than 10,000 pounds per year), but which are selected for T1S during the first phase of the program, would still have to complete the transcriptional activation assays as part of the T1S battery.

It is envisioned that the process of QSAR model expansion and improvement will continue in a cyclical feedback manner, thus providing the opportunity to validate the QSAR models using external data sets for screens and tests of compounds not subjected to HTPS. Eventually, predictions of endocrine disruption potentials obtained from validated QSAR models could be used as surrogates for HTPS data in the case of compounds for which effects data are not available.

J. Inclusion of Mixtures and Naturally Occurring Non-Steroidal Estrogens and Recommendation for a Nominations Process

The EDSTAC recommends in subsequent sections of this chapter that EPA include a discrete number of mixtures (Section VII) and naturally occurring non-steroidal estrogens (Section VIII) in the EDSTP. In addition, the EDSTAC recommends that a process, separate and distinct from the core priority setting process, be conducted to allow affected communities and members of the public to nominate chemicals for screening and, if necessary, testing (Section IX).

K. Introduction of the Endocrine Disruptor Priority Setting Database (EDPSD)

The PSWG struggled with how to use the information sources and criteria it identified to sort and prioritize chemicals for endocrine disruption screening and testing. The EDSTAC, in response to work group information and queries, directed the PSWG to consider developing a computer database to electronically store information related to criteria that could be used for sorting and prioritizing. The EDSTAC was careful to instruct the PSWG not to develop a list of what were then referred to as "high priority chemicals for Phase I screening," but rather to develop a tool to illustrate different scenarios that could show the implications of alternative choices for setting priorities.

The PSWG asked two of its members to develop a relational database containing information sources associated with various criteria to facilitate the sorting and prioritizing processes. The resulting prototype database is referred to as the Endocrine Disruptor Priority Setting Database (EDPSD). A preliminary version of the EDPSD was presented to the EDSTAC in December 1997.

The EDSTAC was impressed by the speed with which the EDPSD could provide different scenarios, and gave unanimous support for continued development of the EDPSD. However, it became clear that sufficient time and resources were not available to adequately develop the EDPSD within the time frame of EDSTAC's deliberations. Accordingly, the PSWG was told that EPA would complete and validate the EDPSD as a post-EDSTAC exercise. Section X of this chapter provides a more detailed description of the prototype EDPSD, including the data fields that were included by the December 1997 plenary, the data fields the EDSTAC recommends that EPA include, and a process for using the EDPSD.

L. Overview of the Recommended Approach to Priority Setting

In Section XI of this chapter, the EDSTAC presents its recommendations for how to set priorities: (a) for chemicals that will need to be considered for T1S, and (b) for chemicals that meet the criterion for bypassing T1S and going directly to T2T. The recommended approach for setting priorities for the approximately 62,000 chemicals that will need to be considered for T1S builds upon the EDSTAC's recommendations to: screen mixtures and naturally occurring non-steroidal estrogens; establish a separate and distinct nominations process; separate out food-use pesticides and other chemicals that have sufficient data to bypass T1S; and utilize a database tool to help analyze information relevant to priority setting. The recommended approach is one that would have EPA, with continued advice and assistance from a multi-stakeholder group, use the EDPSD to help set priorities that flow from a simple and transparent application of the exposure- and effects-related information categories and criteria. The EDSTAC recommends that EPA apply the information categories and criteria outlined in Sections III and IV in a manner that would explicitly state the percentage of the total number of chemicals to be subjected to T1S in any one phase of the program to be drawn from the data sources for each criterion, or from the explicit combinations of criteria. This approach, which is referred to as a "compartment-based" approach to priority setting, is described in more detail in Section XI.

The recommended approach for setting priorities for chemicals that meet the criterion for bypassing T1S and going directly to T2T, in the case of food-use pesticides, is to use the schedule EPA has established for tolerance reassessments and pesticide re-registration under the FQPA. All other chemicals that meet this criterion would be addressed on a case-specific basis.

III. Exposure-Related Information and Criteria

This section describes in more detail the types of exposure-related information and criteria that the EDSTAC recommends be used as the foundation for the priority setting process for T1S. Exposure-related information and criteria consist of four exposure information categories and one fate and transport information category.

The four exposure-related information categories are: (a) biological sampling data for humans and other biota; (b) environmental, occupational, consumer product, and food-related data; (c) data on environmental releases; and (d) data on production volume. These four exposure-related information categories can be viewed as a hierarchy or spectrum in an exposure chain. At one end of the exposure spectrum is the detection of chemicals in animal or human tissues and/or fluids via biomonitoring studies. Such detection indicates that systemic exposure has actually occurred. Detection of a chemical in an environmental medium, or knowledge that a chemical is in food or a consumer product, indicates it is probable that exposure can occur. Knowledge that a chemical is released to the environment indicates that, depending upon its physical and/or chemical properties, exposure is possible. Production volume data show that a given chemical is produced and could be released to the environment and exposure may occur. At the other end of the spectrum, some chemicals are entirely consumed in making a subsequent product (e.g., in a

closed system) and, thus, are never released to the environment. Regardless of which data are used, special attention should be paid to chemicals for which there is evidence of embryonic, *post partum* or post hatch, early life stage, or pre-maturation exposures.

A major limitation of the more direct measures of exposure is that data are available for only a limited number of chemicals. Human exposure information is not currently collected for the purpose of priority setting and/or risk assessment. Data that do exist have been collected for other purposes. U.S. population exposure data that exist from the Centers for Disease Control and Prevention are limited to some heavy metals, volatile organic compounds, persistent organochlorines, and some non-persistent pesticides. The ongoing National Health and Nutrition Examination Survey (NHANES) family of surveys (see Appendix G) does provide an opportunity to sample human tissue for additional chemicals. However, funding for analysis of the NHANES samples has not been secured. In contrast, while production data exist for a large number of chemicals, the link between production data and exposure is tenuous.

The fate and transport information category includes chemical and/or physical properties that may be used to predict or estimate the medium or media where a chemical is likely to be found and whether or not a chemical is likely to remain in the environment over time. This information can be used in several ways. Since new chemicals will not have any data in the four exposure-related information categories, the fate and transport information, along with estimates on production volumes or environmental releases can be used to estimate concentrations in environmental media. Fate and transport information can also be combined with known production volumes or environmental release information to estimate concentrations in environmental media. The more direct the measure of exposure that is combined with fate and transport information, the more likely one would anticipate the estimates to be of actual conditions. Unlike the other exposure-related information categories which contain measurable empirical data, fate and transport information consists of estimations and predicted and/or calculated data.

The remainder of this section describes in more detail the nature of the information included in each exposure-related information category, the strengths and limitations of the type of information in each category, and a recommended set of guiding principles for how to use the information contained in each category to complete the task of setting priorities for endocrine disruptor screening and testing.

A. Biological Sampling Data

Biological sampling refers to the monitoring of tissues or media from living or dead organisms for chemicals to document actual human or animal exposure. The biological sampling information category includes data that falls into two subcategories: (1) human biomonitoring, and (2) monitoring of other biota. Human biomonitoring refers to monitoring of human tissues and media (e.g., blood, breast milk, adipose tissue, and urine). Monitoring of other biota encompasses the sampling of a very wide range of species (invertebrates, vertebrates such as fish, and other wildlife) and sample matrices (e.g., carcass, liver, kidney, egg, feathers, etc.) for exposure to environmental contaminants.

Strengths

Human

- Data are evidence of actual human exposure
- Many data sets are representative of large populations; other data sets are representative of disproportionately exposed populations
- Can be used to provide data to address mixtures
- Generally good quality data; however, this must be determined on a case-specific basis
- May be used to identify trends
- For those substances monitored, can evaluate frequency and magnitude of exposure detections relative to each other to help prioritize
- Addresses multiple routes of exposure

Other Biota

- Data document actual exposure
- Analytical data sets are generally of high quality
- Multiple routes of exposure are addressed
- Broad coverage of phylogenetic groups (e.g., fish, reptiles, birds, wild mammals, shellfish and other invertebrates, etc.), habitats, and environmental matrices
- Information on various animal species will substantially enhance understanding of the phenomenon of human effects
- Many monitoring programs are spatially and temporally replicated

Limitations

Human

- Limited number of compounds monitored; limited data available may not capture any short-lived compounds or peak exposure
- Biologic half-life, metabolism, and tissue distribution vary from substance to substance
- Limited opportunities to collect appropriate specimens
- May not be representative with respect to time, population, or exposure distribution
- Population surveys (e.g., NHANES) may not characterize particularly susceptible or disproportionately or highly exposed subpopulations (e.g., workers)
- Identified compounds may not be traceable to a particular producer
- Need to separate biomarkers of exposure from those of susceptibility or effect
- Analyses often focus on the “usual suspects” and additional substances need to be measured

Other Biota

- Limited number of compounds monitored; limited data available may not capture any short-lived compounds or peak exposure
- Biologic half-life, metabolism, and tissue distribution vary from substance to substance
- Limited opportunities to collect appropriate specimens
- Population surveys may not characterize particularly susceptible or disproportionately or highly exposed subpopulations
- Identified compounds may not be traceable to a particular producer
  Need to separate biomarkers of exposure from those of susceptibility or effect
- "Exposure" or "potential exposure" are generally monitored; "biological effects" are not

Guiding Principles for Using These Data for Priority Setting

- The greater the relevance of the data set to large populations, disproportionately exposed subpopulations, or particularly susceptible subpopulations, the more weight the data set should be given.
- Data sets with good quality assurance/quality control (QA/QC) data should be given greater weight than those data sets with lower QA/QC data.
- The lower the detection limits and the greater the efforts to test organisms that are likely to be exposed, the greater the weight "non-detect" data should be given.

B. Environmental, Occupational, Consumer Product, and Food-Related Data

Environmental, occupational, consumer product, and food-related data include: (1) monitoring data for chemical contaminants found in a variety of environmental media to which humans and animals are exposed, such as water (surface, ground, and drinking), air, soil, sediment, and food; and (2) use information for chemicals, when it is available.

Strengths

- Provides data on likely exposures to humans and other biota
- Databases exist for air, water, soil, and food
- May be used to identify trends
- Data can be used to identify relevant media for exposures (e.g., food, air, and/or water)

Limitations

- Limited number of compounds monitored
- Quantitative exposure levels must be inferred in many cases
- "Detect" limits may vary from one data set to another
- Use data sources are not comprehensive, are frequently secondary sources, and may not be independently verified. The highest quality, most comprehensive data sources are usually

maintained by fee-for-service organizations. Consequently, no use information databases for existing chemicals have been included in the EDPSD.

Guiding Principles for Using These Data for Priority Setting

- The greater the relevance of the data set to large populations, disproportionately exposed subpopulations, or particularly susceptible subpopulations, the more weight the data set should be given.
- The more likely a chemical is to be internalized by an organism from its environment, the greater weight it should be given.
- Data sets with good QA/QC data should be given greater weight than those data sets with lower QA/QC data.
- The lower the detection limits and the greater the efforts to test organisms that are likely to be exposed, the greater the weight "non-detect" data should be given.

C. Environmental Releases

Environmental release information includes data on chemicals released to the environment to which humans and animals may be exposed, such as permitted industrial discharges to air or water and accidental release or spill data. An example of the industrial discharge data is the Toxic Release Inventory (TRI) reporting required by EPA. An example of accidental release or spill data is the Hazardous Substance Emergency Surveillance System maintained by the Agency for Toxic Substances Disease Registry (ATSDR).

Strengths

- Provides data on potential and known exposures to humans and other biota
- Databases exist for air and water
- May be used to identify trends
- Data can be used to identify relevant media for exposures (e.g., food, air, and/or water)
- TRI is updated annually
- Databases include location-specific data which are relevant to disproportionately exposed populations

Limitations

- Data exist for a limited number of industrial chemicals (528 in the case of the TRI)
- Quantitative exposure levels are difficult to estimate in many cases
- No data are available in the TRI for releases under 10,000 pounds per year from single sources

Guiding Principles for Using These Data for Priority Setting

- The greater the relevance of the data set to large populations, disproportionately exposed subpopulations, or particularly susceptible subpopulations, the more weight the data set should be given.
- The more likely the environmental releases are to lead to organism exposure, the greater the weight the release data should be given (e.g., TRI releases to air and water should be given more weight than TRI releases to disposal such as permitted landfills, etc.).

D. Production Volume Data

Production volume data include production information, primarily volume, for chemical substances and are mainly relevant to existing chemical substances. Such information can only be estimated for new products and is not relevant to environmental contaminants. The discussion of strengths and limitations which follows distinguishes among existing industrial (i.e., TSCA-regulated) chemicals, existing pesticides (i.e., FIFRA-regulated), and new chemicals.

Strengths

Existing Industrial Chemicals (TSCA-Regulated)
- Quick, easy way to obtain a rough estimate of exposure potential
- Readily available (to EPA) for chemicals other than polymers and inorganics produced or imported in amounts greater than 10,000 pounds per year
- Reliable and comprehensive
- Identifies site-limited chemicals
- Excludes non-isolated intermediates
- Includes data on imported chemicals

Existing Pesticides (FIFRA-Regulated)
- Production data available at national level (but not state level) for all covered products only as composite, not manufacturer-specific
- Available to EPA and the public

New Chemicals
- Estimated production volume data available to EPA for all new chemicals
- Comprehensive

Limitations

Existing Industrial Chemicals (TSCA-Regulated)
- TSCA inventory update identifies site-limited intermediates, but does not contain information on uses of individual chemicals
- TSCA inventory data may be protected as Confidential Business Information (CBI), which means that they are available to the EPA but not to the public
- Does not contain data on degradates, mixtures of chemical substances, inorganics, polymers, or chemicals produced/imported in amounts less than 10,000 pounds per year

Existing Pesticides (FIFRA-Regulated)
- Often lacking information on number of potentially exposed workers, "fence-line" concentrations, and environmental release pathways
- Currently contains information on currently registered and used products only

New Chemicals
- TSCA data for new chemicals may be protected as CBI, which means that they are available to the EPA but not to the public
- Production data are estimates
- Many Pre-Manufacture Notification (PMN) chemicals are never commercialized; fewer are commercially successful

Guiding Principles for Using These Data for Priority Setting

- Production volume provides only a very rough indication of potential human and ecological exposure. Combining production data with other data (e.g., effects data) minimizes, to a certain extent, some of the inherent weaknesses of using production data as a surrogate for exposure. Production information should not be used to prioritize between existing industrial chemicals and pesticides or between new chemicals and pesticides because production volume ranges are too divergent. For example, production volumes for high-volume industrial chemicals are several orders of magnitude higher than those for either new chemicals or pesticides.

E. Fate and Transport Data and Models

Environmental fate and transport information is available from various reference sources, including databases, textbooks, and monographs (e.g., Swanson and Socha, 1997; Cowan et al., 1996). Although the data source matrix for environmental fate and transport data and models included in Appendix G highlights a number of specific sources of information, no single source is really superior to another in that each is a collection of data. Because there is a lot of environmental fate and transport data from which to choose, the challenge is to identify the critical fate and transport data useful for sorting and prioritization purposes.

The EDSTAC recommends that EPA focus on three subcategories of environmental fate and

transport information: persistence, mobility, and bioaccumulation. Each of these factors can affect the bioavailability of a chemical substance because each is directly correlated to potential exposure. The definitions used by the EDSTAC for these terms are as follows:

> **Persistence** is the tendency of a chemical substance or its degradation products to persist (survive) in the environment without transformation into another chemical form.
>
> **Mobility** is the tendency of a chemical substance to move within environmental media (e.g., air or water) or between media (e.g., to migrate from soil to groundwater).
>
> **Bioaccumulation** is the capacity of a chemical to accumulate (be stored in the tissue) in an organism as a result of uptake from all environmental sources.

Strengths

- Environmental fate and transport tests pertaining to the three categories are already in place and have a long history of use for many chemicals
- EPA has identified thresholds for various environmental fate and transport tests that trigger regulatory concern; however, at this time, the quantification of these potential thresholds (or "triggers") and their application to determine the potential for endocrine disruption may be lacking or subjective
- Modeling can also be used to estimate environmental fate and transport characteristics of persistence, bioaccumulation, and mobility when test data on specific substances are lacking

Limitations

- No single source of information on fate and transport includes all chemical substances
- There are gaps in the data sources, making direct comparisons between chemical substances difficult
- Most fate and transport estimating procedures have not been validated over the range of possible chemical substances that will need to be considered for endocrine disruptor screening and testing
- Test data for the three selected parameters may not be available for all chemical substances
- At this time, there are no generally established or accepted environmental fate or transport criteria directly related to endocrine disruption
- Fate and transport of chemical substances may vary widely depending on environmental conditions; arbitrary standard conditions are established for regulatory and comparative purposes

Guiding Principles for Using These Data for Priority Setting

- For each of the three environmental fate and transport characteristics – persistence, mobility, and bioaccumulation – the tables contained in Appendix H specify relevant physicochemical criteria along with their corresponding threshold (or "trigger"). These "triggers" are those which EPA generally takes into consideration when evaluating a pesticide or chemical for

registration. However, it should be noted that EPA does not rely solely on "trigger" values, but considers other environmental effects (e.g., wildlife toxicology) before granting product registrations.

- The use of fate and transport data to help set priorities for T1S should take into account all three environmental compartments – air, water, and soil.
- Fate and transport characteristics should be based on laboratory or field tests when good quality data are unavailable. If laboratory or field data are lacking for a chemical, EPA should calculate the predicted fate and transport data for use in priority setting by means of reliable methodology or by use of an algorithm.
- The physicochemical measures recommended for each of the three environmental fate and transport characteristics identified above – persistence, mobility, and bioaccumulation – are listed below:

    - Hydrolysis half-life – persistence;
    - Biodegradation – persistence;
    - Photooxidation – persistence;
    - Volatility (Henry's Law) – mobility;
    - Absorption Coefficient (K_{oc}) – mobility; and
    - Octanol:Water Partition Coefficient (K_{ow}/LogP) – mobility and bioaccumulation.

- Fate and transport measures that provided redundant information were eliminated. Some measures, such as photolysis, must be determined experimentally. A surrogate measure, photooxidation in this case, can help to fill gaps in the data (photooxidation is one estimate of the atmospheric half-life of a parent compound due to reaction with photochemically-produced hydroxyl radicals).

IV. Effects-Related Information and Criteria

In addition to HTPS, which is described separately in Chapter Four, Section V, the effects-related information categories the EDSTAC recommends as the foundation for the priority setting process include: (a) toxicological laboratory studies and databases; (b) epidemiological and field studies and databases; and (c) predictive biological activity or effects models, commonly referred to as Structure Activity Relationship (SAR) and/or Quantitative Structure Activity Relationship (QSAR) models.

Toxicological laboratory studies and databases include all published, publicly available, or otherwise useable information related to the laboratory study of toxic effects of chemical substances and mixtures on living organisms or cell systems, including humans, wildlife, and ecological systems.

Epidemiological and field studies and databases range from hypothesis-generating descriptive studies, such as case reports and ecological field analyses, to prospective cohort studies and rigorously controlled hypothesis-testing clinical trials or community interventions. The most

common studies are descriptive.

Empirical toxicological and epidemiological data are reported in a large number of peer reviewed scientific journals. Published studies are conducted with varying degrees of methodological rigor and data are reported in widely varying detail. Consequently, information obtained from the general literature must be reviewed in detail in order to determine its applicability and adherence to generally acceptable investigatory practices. Some positive reproductive effects data are included in several regularly updated databases which are described in more detail in Appendix G.

Predictive biological activity or effects models attempt to identify correlation between properties that can be derived from the chemical structure or properties of molecules and biological activities, including those that can be identified through *in vitro* or *in vivo* screens and tests. SAR and QSAR models are also used to predict physicochemical properties such as solubility, volatility, and lipophilicity (LogP). QSARs are useful for estimating or predicting how a chemical may behave when empirical toxicological or epidemiological data are unavailable.

General Guiding Principles for Effects-Related Criteria

- The EDSTAC believes that using published toxicological laboratory, epidemiological, or field studies for priority setting without first narrowing the universe of chemicals subject to detailed review would be virtually impossible in the appropriate time frame and with available resources. Accordingly, the EDSTAC recommends that data from the general scientific literature, which is not organized into logical databases, be used to help set priorities *after* an initial selection is made based on effects-related data organized into logical databases. This issue is discussed in more detail in Chapter Four, Section X, E.
- QSAR models should not override HTPS information. Rather, HTPS data should be used to improve the QSAR database as described more fully in Chapter Four, Section V, G, 3.
- Positive epidemiological studies should be considered of higher value for priority setting purposes even in the presence of negative toxicological studies.
- EPA has provided considerable guidance on how to interpret the results of toxicity, epidemiology, and other relevant data. This guidance should be relied upon in interpreting the available database for prioritizing effects information. The most relevant guidance for endocrine disruptor information are the Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), the Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996), and the Guidelines for Neurotoxicity Risk Assessment 1998.

The remainder of this section describes in more detail the nature of the information included in each effects-related information category, the strengths and limitations of the type of information in each category, and a recommended set of guiding principles for how to use the information

contained in each category to complete the task of setting priorities for endocrine disruptor screening and testing.

A. Toxicological Laboratory Studies and Databases

Strengths

- For a few chemicals, particularly those regulated under FIFRA, a wide variety of whole animal studies have been completed using modern protocols with some endocrine sensitive endpoints (e.g., developmental toxicity, reproductive toxicity) and conducted under Good Laboratory Practices (GLPs)
- Allows for testing of single agents and/or mixtures to establish cause-and-effect relationships
- Studies are likely to provide useful dose-response data for the endpoints and species studied
- Good coverage for a few chemicals and/or substances (e.g., petroleum crudes, organochlorine pesticides) with respect to aquatic species, birds, and wildlife

Limitations

- Toxicological database for industrial chemicals is less complete than that for pesticides
- Ability to extrapolate endocrine-related knowledge in test species to other species, including humans, is limited by the lack of knowledge about interspecies comparative endocrinology
- Effects at very low doses and the presence of an inverted "U-shaped" dose-response curve or the "inverted J-shaped" curve indicative of hormesis have generally not been examined in toxicological studies
- Studies may not be designed to detect the relevant endpoints
- Relevance of *in vitro* data to organisms and populations is not well characterized
- Very little data on TSCA-related chemicals especially for effects on birds and fish
- Little is known of endocrine disruptor effects in wild mammals, lower vertebrates, and invertebrates
- Relatively few studies have looked at subtle and multi-generation effects

Guiding Principles for Using These Data for Priority Setting

- Whenever possible, *in vivo* studies with relevant endpoints and with wide dose-response data should be viewed as more relevant for priority setting than *in vitro* studies. This is especially true when considering *in vitro* studies featuring receptor-mediated mechanisms, which typically do not correlate well with endocrine-mediated *in vivo* effects.
- Studies that have any or all of the following characteristics should be valued greater than those that do not:
    - inclusion of relevant endpoints sensitive to endocrine disruption
    - indication of a dose response for endocrine disruptor effects
    - receipt of peer review
    - GLP compliance

B. Epidemiological and Field Studies and Databases

Strengths

- These data may provide actual observation of impacts upon humans, organisms, or ecological communities, removing many of the uncertainties inherent in assessing risk based on laboratory studies
- When these data include biomarkers of exposure or effects, they can serve to document a completed exposure pathway
- Data from these studies can provide information on vulnerable populations or high-exposure subgroups, such as the occupationally exposed

Limitations

- Human disease and organ system dysfunction is multifactorial in causality, making it difficult to identify the contribution of individual factors unless they are dominant causes
- The mechanisms which lead to specific human diseases are often unknown, and the specific endocrine disruption mechanisms which cause specific diseases are poorly understood
- Small excess risks for common health outcomes may be difficult to identify without appropriate consideration of study power.
- Studies of highly exposed individuals may not be relevant to much lower population exposures or to more vulnerable subpopulations; extrapolation of high-exposure effects to low-exposure circumstances or between subpopulations introduces uncertainty and decreases the utility of the data
- Studies often address only one route of exposure; this route, however, may not be the most relevant route for the general population
- Human and ecological communities are seldom exposed to only one compound; it is difficult to identify and examine the effects of multiple exposures and their possible interactions

Guiding Principles for Using These Data for Priority Setting

- Despite the many limitations inherent in epidemiological and field study data, statistically positive studies should be a priority indicator for additional screening and testing.
- When multiple studies exist and there is a consistently positive association between exposure and an effect, but individually the studies do not reach statistical significance, this finding should be given weight when determining the priority for screening and testing.
- Weight given to statistically negative studies should be dependent upon the study design, quality of the data, and the power of the study to detect an effect. Negative human epidemiological studies and ecological field studies should be considered, but should not necessarily override positive toxicological studies when determining priority for screening and testing.
- When multiple studies exist, weight should be given to those studies that have received peer review and which are of high design quality. A checklist of issues important to evaluating a

study should be developed to assist in the review. Such a checklist would include likelihood of misclassification of exposure or disease, likelihood of introduction of bias, and utilization of standardized tools or methods.

- Descriptions of studies should include a characterization of their design. Study design is important in determining the inferences that can be drawn from the results. Commonly used descriptors include: descriptive (case reports, case series, calculations of rates of prevalence, incidence, mortality); observational (ecological, cross-sectional, case-control, cohort, proportionate morbidity/mortality ratio); and experimental (clinical trial, community trial).

C. Predictive Biological Activity or Effects Models

Strengths

- SARs/QSARs can be used to rapidly and relatively inexpensively predict biological activities of large numbers of compounds, thereby avoiding the need to prioritize on the basis of "no data"
- Current SAR/QSAR models developed for application to endocrine disruption analysis predict binding affinity and, therefore, have the same advantages and disadvantages as the *in vitro* models upon which they are based
- The use of SARs/QSARs in sorting and prioritizing allows for transparency and comparative consistency and avoids the problem of comparing different experimental data types against each other (e.g., two-generation reproduction study versus *in vitro* binding)

Limitations

- No models are perfect, and the current receptor binding models suffer both from the imperfections of receptor binding modeling and the ability of receptor binding to predict *in vivo* activity
- Not all mechanisms of endocrine disruption are known or have enough data to model; it is, therefore, not possible to generate models for all possible ways in which the endocrine system can be disrupted

Guiding Principles for Using These Data for Priority Setting

- Guiding principles applicable to the biological effects data used as the basis for the SAR, as well as to the QSAR itself, should be applied to the results of the SAR/QSAR.
- The applicable chemical domain of the SAR/QSAR should be as diverse as possible.
- SARs/QSARs should be developed using the most complete and accurate data sets available.
- SARs/QSARs should be validated and used only within the range of conditions for which they are validated.

V. High Throughput Pre-Screening

A. Introduction

During the course of its investigations the EDSTAC realized that, with the exception of food-use and consumer pesticides with regulatory mandates requiring developmental and two-generation reproductive toxicity testing, substantial endocrine effects data were lacking for most chemical substances. Developmental and reproductive toxicity screening and testing data are available in the literature for an estimated 5,000 chemicals, a large fraction of which are pesticides and pharmaceuticals (John D. Walker, U. S. EPA, personal communication). In addition, existing QSAR methods for endocrine-mediated effects are presently insufficiently validated to be universally accepted as a source of effects data (Ankley et al., 1997).

In the absence of biological effects data, the scientists and officials within EPA charged with carrying out the priority setting process will be left with the choice of either raising or lowering the priority of a chemical based on a lack of effects information. Raising the priority seems to make sense from a public health protection standpoint, but in reality it will accomplish nothing because the vast majority of chemicals being evaluated are likely to be in the "no data" category for endocrine-mediated effects. In essence, if a lack of data became a rationale for making a chemical a high priority for screening and testing, it could render the biological effects portion of the prioritization process meaningless.

To address the problem of having little or no endocrine disruptor effects data on the majority of chemicals that will need to be screened and possibly tested, the EDSTAC recommends that EPA use "high throughput pre-screening" (HTPS). As the term is used throughout this document, HTPS refers to the use of automated processes (robotic and specialized instrumentation) to aid in the screening of compounds. These automated processes involve a number of preparatory operations, some of which are also associated with traditional screening approaches, such as sample preparation (weighing and dissolving in the appropriate medium), screening, and the reading of screening results. However, in the case of HTPS, the process of placing the samples into a microliter plate, the sampling process itself, and the reading of sampling results, are all automated. Since all processes are automated and can be programmed to run continuously, it is possible for large numbers of samples to be assayed in a relatively short period of time using this technology.

High throughput screening technology is used extensively in the pharmaceutical and agrochemical industries to identify chemicals that have commercial potential or that may have desirable or undesirable biological effects (Christopher Waller, OSI Pharmaceuticals, Inc., personal communication). The EDSTAC proposes that high throughput screening technology be employed as a prioritization tool – hence the term "pre-screening" – for the endocrine disruptor screening and testing program. HTPS results, although limited in the scope of information they generate, will be useful in identifying chemicals that have an affinity for the estrogen, androgen, or thyroid hormone receptor. This information could be used in conjunction with other exposure- and effects-related information to determine the priority by which chemicals should be advanced

to the screening and testing tiers of the program. However, HTPS results will *not* be sufficient to make a definitive determination about whether a chemical does or does not have endocrine disrupting properties. This is the function of T2T.

The EDSTAC's recommendations regarding HTPS are contingent upon the demonstration of feasibility of this process in the context of the EDSTP. Appendix I contains information on the demonstration of feasibility proposal. The remainder of this section explains the purposes of HTPS and how it will be used to improve the endocrine disruptor priority setting, screening, and testing processes. Chapter Five describes some of the HTPS assays in more detail and their relation to the other assays in the T1S battery.

B. Purpose of HTPS

First and foremost, HTPS will provide a baseline of systematically gathered data for the endocrine hormones that are currently addressed in the program – estrogen, androgen, and thyroid. This is especially important for those chemicals for which such data on endocrine relevant effects are otherwise lacking, namely most chemicals on the TSCA Inventory. The use of HTPS data should make screening more productive, as it is likely that a higher proportion of chemicals sent to T1S during the early phases of the program will have some evidence of biological activity.

Second, given the exploratory nature of HTPS, it is important to gain some perspective on the effectiveness of this methodology compared to other methodologies, such as QSARs, that can be used to identify compounds for screening. There is some concern that pre-screening chemical substances – especially some pesticides, for which substantial reproduction and developmental (whole animal) testing data may already exist – is a redundant exercise.

The EDSTAC recognizes that the inappropriate use of HTPS data could result in a certain stigma or in product de-selection. This potential is not unique to HTPS, but is a broader communication issue related to endocrine disruptor screens and tests in general. This issue is addressed in Chapter Six. EDSTAC members believe that if communication of the results of HTPS is handled effectively, inappropriate use of the data and potential adverse marketplace reactions to such inappropriate use will be minimized.

C. Which Assays Will be Conducted in HTPS?

As noted in Chapter Two, one of the key mechanisms by which chemicals affect the endocrine system is by interacting with receptors. There is substantial evidence to support this statement for estrogen and androgen receptors. Existing data suggest that receptor binding may not be a significant mechanism for thyroid-related effects. As discussed in Chapter Five, both the transcriptional activation and receptor binding assays for estrogen alpha and androgen hormones are recommended for inclusion in the standardization and validation program for T1S. If transcriptional activation assays can be standardized, validated, and shown to be as reliable as receptor binding assays, the EDSTAC recommends that they be included in the screening battery

as the preferred assay to detect receptor interactions. The receptor binding assay is an acceptable alternative that has decades of use, but may be less informative than the transcriptional activation assays in terms of the nature of the interaction (agonism or antagonism). The potential contributions of both types of assays in the context of priority setting are discussed below.

Receptor binding assays are cell-free biochemical preparations in which one determines the amount of chemical that binds to the hormone receptor as a function of the concentration of the chemical in solution, thus determining the affinity of the chemical for the receptor. Because receptor binding assays only measure binding, whether a substance is an agonist (turns on or turns off gene expression like the natural ligand) or an antagonist (which has the ability to block the action of the natural hormone) cannot be determined.

Transcriptional activation assays are conducted with intact cells that have been genetically modified to contain a hormone receptor and a reporter gene. The reporter gene produces a protein that can be quantitatively measured to reflect the ability of a chemical to act like a hormone, or to block the action of a hormone. The chemical may bind to the receptor and the resulting receptor-ligand complex binds to a specific place on the reporter gene called the hormone response element. Subsequent steps include transcription of DNA of the gene to form RNA and translation of the RNA to form the marker protein. There are several different kinds of marker proteins that have been used in these assays. The common property is that they produce detectable signals that gene expression has taken place. For example, one marker protein, luciferase, is derived from fireflies and causes the emission of light when acting on luciferin, which is introduced into the culture medium. Thus, the activity of a hormone mimic is detected by the amount of light produced by the cell. In practice, the amount of light produced can be compared with that produced when the natural hormone or a reference substance is added to the culture.

Transcriptional activation assays incorporate receptor binding, but may be more relevant to responses in whole animals because they use intact cells and measure biological processes that result from receptor binding. However, relevance must be balanced with the fact that, because of the added complexity inherent in these processes, it is possible for the marker protein to be expressed by actions of the chemical unrelated to receptor binding. The cells used may have some ability to metabolize tested chemicals. This metabolic competence can be enhanced by genetically incorporating the ability to make one or more of the enzymes typically involved in metabolism of exogenous chemicals. This may provide the assay with the ability to detect compounds which must be metabolically altered in order to bind to the receptor. These enzymes can also be added to the receptor binding assays.

Both the transcriptional activation and receptor binding assays can be run automatically at several concentrations to determine an EC-50 (the concentration at which 50% response is obtained). The EC-50 can be used to compare potencies of chemicals within each assay, which is a useful index for setting priorities among chemicals for additional screening.
EPA has selected the transcriptional activation assay utilizing the luciferase reporter gene for demonstration purposes and, if shown to be technically feasible and valid, intends to use it for the HTPS. In this assay system the test material is run in the assays listed below with and without metabolic activation for agonist and antagonist potential. Multiple doses (probably five plus a

control) would be run so that an EC-50 for transcriptional activation can be determined as a measure of potency as discussed above.

1. Estrogen Alpha Receptor Transcriptional Activation Assay (no metabolism)
2. Estrogen Alpha Receptor Transcriptional Activation Assay (metabolism)
3. Estrogen Beta Receptor Transcriptional Activation Assay (no metabolism)
4. Estrogen Beta Receptor Transcriptional Activation Assay (metabolism)
5. Androgen Receptor Transcriptional Activation Assay (no metabolism)
6. Androgen Receptor Transcriptional Activation Assay (metabolism)
7. Thyroid Receptor Transcriptional Activation Assay (no metabolism)
8. Thyroid Receptor Transcriptional Activation Assay (metabolism)

D. Limitations of the Assays to be Conducted During HTPS

There are two noteworthy limitations to the types of assays being considered for the HTPS step. First, these assays cover only one of the possible mechanisms of action for endocrine-mediated toxic effects. At present, this includes biological activity resulting directly from the binding of a chemical to the hormone receptor. On the other hand, existing data on thyroid-active substances (other than the natural ligand) have *not* shown that thyroid receptor binding/activation is a key component of the mode(s) or mechanism(s) of action by which that substance exerts its thyroid-related effects. Nonetheless, the HTPS will include the thyroid receptor transcriptional activation assays. This will be done for two reasons: (1) to do so will constitute only a minor increase in cost and effort; and, perhaps more importantly, (2) to confirm or refute the current hypotheses. If the results of HTPS show that thyroid receptor binding/activation is a key component of the mechanism(s) of action, then thyroid receptor assays would be included in the basic T1S battery.

Assays that assess the activity of enzymes involved in hormone synthesis are technically possible to conduct using high throughput technologies but are not being recommended for inclusion in HTPS by the Committee. Despite this limitation, there are good scientific reasons to believe that most androgen- and estrogen-mediated toxicants capable of eliciting adverse effects at low doses do so by binding to a receptor. Therefore, the overarching goal of protecting human and ecological health is likely to be served by evaluating this mechanism early in the EDSTP.

The second significant limitation of the assays being considered for use in the HTPS step of the process is that they are unlikely to produce the same spectrum of metabolites that an intact animal produces. That is, chemicals that need to be metabolized in order to be active may not be detected by HTPS. Again, this limitation will be addressed in the screening tier. Both of these limitations will also need to be considered in the interpretation and utilization of the results of HTPS for purposes of priority setting.

E. Technical and Logistical Issues

Estimates of the speed of using high throughput technology are encouraging. Once the

preliminary collection and handling of the chemicals are completed, it is not out of the question for several thousand assays to be run in one month, depending on whether confirmatory assays are also run (Christopher Waller, OSI Pharmaceuticals, Inc., personal communication). However, there are technical and logistical constraints, as well as policy issues, that will need to be addressed in determining the number of chemicals that can or should be subjected to HTPS.

With regard to the technical constraints, some compounds have physical and/or chemical characteristics such as insolubility, high volatility, and high reactivity that are not amenable to any *in vitro* screening system. There are, however, scientific reasons to assume that highly insoluble and highly reactive chemicals are unlikely to be endocrine disruptors.

There are also some significant, but not insurmountable, logistical hurdles to be overcome. One so-called hurdle includes validation of the assays for the significantly diverse kinds of chemicals that will be subjected to HTPS. While it is intended, and expected, that HTPS will provide some false positives while minimizing false negatives, there is currently no history of use for HTPS methodology to evaluate large numbers of diverse chemical substances for potential endocrine-mediated effects. Until now, HTPS endocrine assays have been used mainly as a tool to identify new leads or to assess biological activity of an existing lead. The possibility exists that HTPS may not provide sufficient effects data to warrant continued use, or that it may result in an unacceptable number of false negatives. However, all screens, whether automated or not, must undergo the process of validation.

In addition to validation, the problem of obtaining the chemicals must be overcome before HTPS can be implemented. This process involves not only collection but quality assurance of the collected samples. Some chemicals in the environment (e.g., NONEs) are simply not commercially available. Moreover, since there is no registrant or chemical manufacturer for such "orphan" chemical substances, the ownership and responsibility to shepherd them through the screening and testing processes will rest with EPA or other government agencies. Obviously, if chemical substances cannot be procured they must either be isolated or synthesized in order to be screened and, if necessary, tested. At this time, the EDSTAC is not aware of how many compounds could fall into this category.

EPA has launched a feasibility demonstration effort designed to ensure that the types of assays being considered for HTPS can be used on the wide range of chemicals that will need to be subjected to this step in the process. For more information on the HTPS feasibility demonstration project, see Appendix I.

F. Which Chemicals Should be Subjected to HTPS?

Although the use of robotic technology will greatly expand the throughput of chemicals over a given period of time for the selected assays, the EDSTAC is *not* recommending that all chemicals needing to be prioritized for T1S be subjected to HTPS. Rather, the EDSTAC recommends that the set of chemicals currently produced in an amount equal to or greater than 10,000 pounds per year (estimated to be about 15,000 chemicals) should be subjected to HTPS. Also, it is expected

that *all* pesticides (i.e., all pesticide active ingredients and formulation inerts) will be subjected to HTPS. As indicated earlier the EDSTAC makes this recommendation to help EPA avoid an unachievable task that might never be completed. Given the history of TSCA, the EDSTAC believes that 15,000 chemicals is not an insignificant number.

The EDSTAC recommends that chemicals determined to be a high priority for T1S that do not undergo the HTPS assays because they are produced in amounts less than 10,000 pounds per year should still undergo the transcriptional activation assays contained in HTPS. However, rather than using the HTPS process, these lower production volume chemicals should undergo transcriptional activation assays on the bench as part of T1S.

The EDSTAC also recommends that chemicals permitted to bypass T1S and go directly to T2T, as well as those permitted to bypass both T1S and T2T and go directly to hazard assessment (due to functional equivalency of data), be subjected to HTPS. However, as described more fully below, the results of HTPS from these chemicals would not be used to set priorities for T1S.

G. How Will HTPS Results be Used?

1. For Chemicals That Will be Prioritized for T1S

In the context of setting priorities for T1S, the EDSTAC recommends that EPA use the results of HTPS in conjunction with other exposure- and effects-related priority setting information. In other words, HTPS results should be considered along with any other biological effects information that may be available, as well as information on exposure-related considerations (e.g., biological sampling; environmental, occupation, consumer product, and food-related data; releases to the environment; production volumes; and fate and transport models and data).

The HTPS results, by themselves, cannot be regarded as definitively proving or disproving endocrine-mediated toxicity in whole animals. Such determinations can only be made with confidence at the end of the entire screening and testing process. There is concern that the results of HTPS will be over-interpreted because they may be the first data that will be generated in the endocrine disruptor evaluation process. Therefore, it is important to stress the limitations of these assays. Most importantly, the HTPS assays are very simple *in vitro* assays. Like any *in vitro* method, the simplicity that makes the assays attractive for rapid generation of data also limits their reliability as predictors of what might occur in the intact organism. They do not possess all of the complexities of pharmacokinetics, pharmacodynamics, metabolism, and multi-system interactions that are inherent in the whole organism. It is rare for an *in vitro* assay for any toxicity to have better than an 80% concordance with *in vivo* results. For this reason, most *in vitro* assays are used only as a preliminary step of a more comprehensive assessment.

HTPS is primarily useful as a pre-screen to indicate the need for further evaluation, but will not always predict toxicity in whole animals. The HTPS results, coupled with data from the remainder of the screening and testing program will be useful in interpreting whether a chemical evokes endocrine-mediated responses. For these reasons, the EDSTAC strongly recommends

that a negative HTPS result not be used as a basis for placing a chemical into the "hold box." Further, the Committee recommends that a negative HTPS result not be used, in isolation, to decrease the priority of a chemical for screening and testing; nor should a positive HTPS result be the only factor considered in setting priorities for T1S.

2. For Chemicals That Meet the Criteria for Going Directly to T2T or Hazard Assessment

Chemicals that meet the criteria for proceeding directly to T2T or hazard assessment would also be subjected to HTPS according to the EDSTP. However, unlike the large number of chemicals that do not meet these criteria, the results of HTPS from this set of chemicals will *not* be used to help set priorities for T1S.

There are several generic reasons why the EDSTAC recommends conducting HTPS assays on food-use pesticides and other chemicals that have previously been subjected to two-generation reproductive toxicity tests. These generic reasons include: (1) the data generated from the HTPS assays will be valuable in and of themselves, even though they are limited to a single mechanism of action and cannot be used by themselves to determine whether a chemical is or is not an endocrine disruptor; (2) as an ancillary benefit, the data can be used to improve and validate QSARs; and (3) beyond these generic benefits, in the case of food-use pesticides that will complete tolerance reassessments prior to the availability of validated Tier 2 tests, HTPS data can be used, along with other relevant information, to help prioritize whether and, if so, when these chemicals should be subjected to any additional endocrine disruptor testing. The last rationale for recommending food-use pesticides complete HTPS assays is further elaborated upon in Chapter Four, Section XI, H.

There may be concern that it is redundant to subject pesticides and other chemicals to HTPS for which substantial two-generation reproductive and developmental (whole animal) toxicity testing data already exist. However, the EDSTAC believes the value of generating HTPS data outweighs the relatively low cost associated with subjecting these chemicals to HTPS.

3. To Improve QSARs

The EDSTAC recommends that existing QSAR models be rederived and supplemented with data from the HTPS assays, thereby expanding the predictive ability of these models. Thus, when it comes time to set priorities for the first phase of T1S, HTPS data, as well as improved QSARs, should be used along with other relevant exposure and effects data. It is envisioned that the process of QSAR model expansion and improvement will then continue in a cyclical feedback manner, thus providing the opportunity to validate evolving QSAR models using external data sets for screens and tests of compounds not subjected to HTPS. Eventually, predictions of endocrine disruption potential obtained from validated QSAR models could be used as surrogates for HTPS data in the case of compounds for which effects data are not available.

H. Practical Considerations and Constraints to Be Considered in HTPS Implementation

There is widespread agreement that several practical considerations will need to be addressed for HTPS to work as intended. These include:

- Demonstrating the feasibility of HTPS – An important first step in implementing the recommendation of the EDSTAC to incorporate the use of HTPS into the EDSTP is to undertake an effort to demonstrate the feasibility of using this technology for the wide range of chemicals that will need to be considered for endocrine disruptor screening and testing. A detailed discussion of the feasibility demonstration effort that is already underway is contained in Appendix I.
- Collecting, handling, and QA/QC of the chemicals to be tested – The procurement of sufficient quantities of relevant chemical substances, the shipment of these materials, and the assurance of the chemical identity and purity of these chemicals will be the most time consuming phase of HTPS. While these issues are inherent in any of the assays being considered for screening or testing, they must be taken into consideration when planning for HTPS as they are likely to contribute to the cost and time for this step of the program. The EDSTAC recommends that EPA explore the feasibility of creating an archive of a subset of these chemicals, which can be accessed by researchers interested in studying endocrine-mediated toxicity or in validating new screens for endocrine disruptors. This may be particularly important for radio-labeled compounds that are costly to synthesize. There is precedence for such activities, including the EPA Pesticide Repository, the National Institute of Standards and Technology (formerly the Bureau of Standards) in the Department of Commerce, and the NTP chemical repository for the validation of *in vitro* developmental toxicity.
- Patent issues – Many or all of the HTPS assays under consideration are patented and the intellectual property issue must be addressed before implementing any endocrine disruptor screening and testing program. This is unlikely to be a critical issue for a massive screening effort because it is almost certain that such work would be done under contract by the holder of the patent. It may, however, be a significant issue for individual investigators or companies who wish to work with the assays on an investigative basis in their own laboratories. Licensing agreements should be worked out before any final decisions are made.
- Overall costs and specific cost factors – As with all screening assays, the cost of performing an assay needs to be taken into account in selecting which HTPS assays to recommend, as high cost may limit the number of chemicals that can be evaluated.
- Validation of the HTPS assays for the wide range of chemicals that are intended for pre-screening – High throughput screening technology has been used in the pharmaceutical and agrochemical industries to find chemicals with novel and relevant biological activity at high potency, as these are the ones that are likely to be candidates for lead optimization. However, environmental chemicals that have been identified so far as having endocrine-mediated effects typically have low potency. Issues such as how good the assays will be at detecting such chemicals; the limit of detection; and how easily these assays will accommodate a range of chemical properties (such as solubility, pH, and high vapor pressure) can be addressed, but doing so may require some research involving a representative group of chemicals before HTPS

can be implemented on a large scale. Based on the results of using HTPS as a tool for identifying discovery leads, one generally should expect a "hit rate" of 1.8-2.0% for a very weak lead (activity at 100 uM), 0.6% for a weak lead (activity at 10 uM), and 0.15% for an average lead (1 uM) (Christopher Waller, OSI Pharmaceuticals, Inc., personal communication).

Other implementation issues, such as who will be responsible for conducting various parts of the HTPS process, how much each step will cost, etc., are not addressed in this document. However, it is envisioned that EPA will undertake the coordination (and, perhaps, expense) of conducting the HTPS step of the program. It is also assumed that implementing the HTPS process will require EPA to work cooperatively with industry to collect what will be a very large number of chemical samples. Moreover, the issue of "orphan chemicals" – those for which there is no current manufacturer or registrant – is an issue that EPA must address.

VI. Recommendations for Handling Polymers

A. Introduction

This section presents some key issues associated with the prioritization of polymers for endocrine disruptor screening and testing along with several options and a recommended approach for how polymers should be treated.

1. Chemical Nature of Polymers

Polymers are defined in 40 Code of Federal Regulations (CFR) Part 723 as

> *a chemical substance consisting of one or more types of monomer units and comprising a simple weight majority of molecules containing at least three monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units.*

Polymers result from chemical reactions that permit varying numbers of monomers or monomer units and other precursors to be chemically incorporated into the products of the reactions. According to 40 CFR Part 723, the term "monomer unit" means "the reacted form of the monomer in a polymer." That is, the monomer must have formed at least one covalent bond with another like or unlike molecule under the conditions of the relevant polymer-forming reaction.

Polymer molecules typically vary in their degree of polymerization, or the extent to which they have incorporated varying numbers of monomers, oligomers, and other precursors. However, polymer products might be composed of various other substances that usually are not the

result of the polymerization reaction including:

- Residuals – unreacted polymer precursors, monomers, oligomers, and other reactants
- Byproducts – catalyst residues, free-radical initiator byproducts, etc.
- Impurities – precursor impurities, oxidation products, etc.
- Other substances – those that are mixed into the product, such as fire retardants, plasticizers, solvents, inhibitors, fillers, colorants, antioxidants, slip agents, etc.

2. Present Regulatory Status of Polymers

The initial TSCA Inventory (or Initial Inventory), published in 1979, consisted of those chemicals that were manufactured in the U.S. or imported into the U.S. on or after January 1, 1975, and before the end of the initial reporting period (which varied depending on the chemical and/or company circumstances). Certain allowances were made for later additions and corrections. The Initial Inventory contained about 60,000 chemicals, approximately half of which were polymers. Chemicals on the Initial Inventory are referred to as "existing chemicals." Chemicals not on the Initial Inventory are considered "new" and are subject to the Pre- Manufacture Notification (PMN) requirements of TSCA. After EPA completes the pre-manufacture review of a new chemical and when the manufacturer or importer of the chemical notifies the Agency that manufacture or importation has commenced, EPA adds the new chemical to the Inventory.

The existing chemical polymers are described in the Initial Inventory using a simplified procedure for naming the polymers. Polymers on the Initial Inventory are named as "Polymer of A, B, C, D..." where A, B, C, D... are the monomers which are reacted to form the polymer. The Inventory chemical name does not include any description of the chemical identity of the specific polymer or polymers that are made from these monomers. For example, there is no information about whether the polymer is in the form of a carbamate, amide, isocyanate, or some combination of these functional groups; nor is there any mention of the presence or absence of reactive functional groups, such as isocyanate or epoxy groups. In addition, the number average molecular weight (NAMW) – which refers to the arithmetic average (mean) of the molecular weight of all molecules in the polymer – distribution of the polymer or polymers made from the listed monomers is not reported. The Initial Inventory, however, does include a number of low NAMW oligomers (dimers, trimers, etc.) which are purposefully manufactured as such.

In contrast to the estimated 30,000 polymers reported on the Initial Inventory (John Walker, U.S. EPA, personal communication), new chemical polymers that are reported to EPA include a chemical description of the polymer containing information on the NAMW distribution, the presence of reactive functional groups, etc. In addition, EPA receives information on the anticipated uses, exposures (occupational, environmental, consumer, etc.), and environmental releases of the new polymers.

The EPA, under TSCA, first proposed the exemption of certain polymers (NAMW greater than 20,000 daltons) from PMN in 1982 (47 Federal Register (FR)). The Final Rule for this early exemption was published in 1984. In making its no-risk finding, EPA concluded with regard to polymers that:

> *Molecular weight is clearly the prime determinant of risk. For a chemical to elicit a toxic response within an organism, it must come into direct contact with the biological cells from which it elicits the response. Because all organisms are encased in protective membranes, a chemical must penetrate these membranes and be translocated to various parts of the organism to gain access to its target sites. If a chemical cannot penetrate the protective membranes to access a target site, and it cannot elicit a toxic response, it will not generally present a risk.* (49 FR 46081, also cited in 60 FR 16328)

EPA operated with this exemption for almost a decade until a proposal to expand the exemption was made in 1993 (58 FR). That proposal was published as a final rule in 1995, and it sets out the exemption policy under which the TSCA program now operates (60 FR). EPA extensively reviewed over 10,000 polymers from 1980 to 1995 and concluded that:

> *Of these 10,000, the polymers that would have qualified under the final polymer exemption rule [1995] have consistently been characterized as posing low concern for both adverse health and environmental risks by the Agency during the course of PMN review. The characteristics of a significant number of polymers (i.e., their NAMW and/or physical/chemical properties) are such that they are neither absorbed by biological systems nor do they interact with biological systems, as described above.* (60 FR 16329)

As required by section 5(h)(4) of TSCA, the current polymer exemption is based wholly on a finding by the EPA that the:

> *manufacture, processing, distribution in commerce, use, and disposal of new chemical substances meeting the revised polymer exemption criteria will not present an unreasonable risk of injury to human health or the environment under the terms of the exemption.* (60 FR 16316)

The present regulation (60 FR 16333) exempts:

- polymers with average NAMW between 1,000 and 10,000 daltons if they do not contain other than certain specified reactive functional groups (as well as containing less than 10% oligomers with NAMW less than 500 daltons and less than 25% oligomers with NAMW less than 1,000 daltons);
- polymers with average NAMW greater than 10,000 daltons (and less than 2% oligomers with NAMW less than 500 daltons and less than 5% oligomers with NAMW less than 1,000 daltons);
- polyester polymers made with any of a long list of specified reactants; and
- polymers produced in quantities less than 10,000 kilograms per year.

Polymers that are *ineligible* for the exemption include:

- polymers that degrade, decompose, or depolymerize;
- polymers that are prepared from monomers or other reactants that are not on the TSCA Inventory; and
- water-absorbing polymers with NAMW greater than or equal to 10,000 daltons.

B. Key Issues Associated With the Prioritization of Polymers

The PSWG originally considered exempting polymers with a NAMW greater than 1,000 daltons from priority setting, similar to the reporting exemption which exists for new chemical polymers under TSCA. All polymers with a NAMW less than 1,000 daltons would be treated like all other chemicals and would be subjected to priority setting. The exempt polymers would be put into a "hold box" pending information on monomers or other low NAMW polymers of potential concern and screening and testing of the monomers themselves. However, concerns surfaced within the PSWG upon further examination.

Bioaccumulation/Potential Exposure

The original proposal to exempt polymers was based on an assumption that molecules larger than 1,000 daltons would not cross biological membranes and barriers. If a neonate is orally exposed to a polymer with a NAMW greater than 1,000 daltons, some of the polymer could enter the body and interact with cells. Such an interaction is unlikely to occur in a more mature animal but could occur in neonates due to delayed intestinal closure. Gastrointestinal absorption is dependent on factors such as lipophilicity, molecular weight, particle size, and metabolism of chemicals in the gastrointestinal tract (Baintner, 1986; Kleinman and Walker, 1984; Lecce and Broughton, 1973; Walker, 1978; Westrom and Tagesson, 1989; Westrom, Svendsen, and Tagesson, 1984; Weaver, Laker, et al., 1987; Westrom, Tagesson, et al., 1989).

The potential for gastrointestinal absorption of high molecular weight substances was taken into consideration by the EPA as early as 1982. The Agency concluded that:

- Substances with NAMW greater than 1,000 daltons are generally not readily absorbed through the intact gastrointestinal tract. (49 FR 46081);
- "For a chemical to elicit a toxic response within an organism, it must come into direct contact with the biological cells from which it elicits the response. Because all organisms are encased in protective membranes, a chemical must penetrate these membranes and be translocated to various parts of the organism to gain access to its target sites. If a chemical cannot penetrate the protective membranes to access a target site, and it cannot elicit a toxic response, it will not generally present a risk." (49 FR 46081, also cited in 60 FR 16328)
- Dermal exposure, rather than inhalation or ingestion, is the major route of exposure for most polymers. (47 FR 33930)

Based on the available data, EPA was able to proceed in making its no-risk finding as a basis for the polymer exemption. The physical properties of a polymer affect not only its functional ability, but its fate and transport in the environment. Generally, as the molecular weight and degree of polymerization increase, the affinity for adsorption to solids (soil and sediment) increases and the potential for biodegradation and bioaccumulation decreases.

Polymer Complexity

Polymers are complex substances consisting of additives such as fire retardants, antioxidants, slip agents, colorants, residual monomers, catalysts, additive reaction products, catalyst residues and reaction products, byproducts, low molecular weight polymer chains, etc. Although additives, monomers, catalysts, many oligomers, and many other substances will be included in the priority setting scheme, some of the other polymer components may not be. Concern about their toxicity arose on the part of the PSWG after reviewing some work done in the early 1970's on a complex polymer fluid showing that the fluid's polysiloxane dimers and trimers were more toxic components of the mixture than were the monomers. Although the issue was not one of incomplete breakdown products, but rather of intentionally made dimers and trimers, the work highlighted the fact that by only studying the monomer, it is conceivable that one might miss a higher order of toxicity reached in the dimers, trimers, etc. The toxicity of these other polymer components may not be the same as the toxicity of the monomers. Thus, testing data from the monomers and additives may not provide complete guidance as to the toxicity of the entire polymer.

Composition of Copolymers

Most polymers, for regulatory purposes, are described and assigned Chemical Abstracts Service Registry Numbers (CASRNs) on the basis of the monomers used in their manufacture. For polymers having multiple monomers (or copolymers, as opposed to homopolymers), the relative concentrations of the various monomers can vary widely, but the polymers can still be assigned the same CASRN. For example, poly(A/B) with an A/B ratio of 95/5 or 5/95 is still described by the same CASRN. Consequently, for purposes of prioritizing polymers for testing, the CASRN does not represent a unique chemical composition.

In addition, for many condensation polymers, chemically identical polymers can be made from slightly different monomers. In this instance, the CASRN would be different, even though the polymers are compositionally indistinguishable.

The variable compositions within a CASRN listing, and identical compositions for different CASRN listings, are problematic for both new polymers, as well as for those nominated to the original Inventory.

Testing of Polymers

Many polymer components do not have an identity apart from their role as a component of a polymer. Hence, they do not exist independently and, in general, cannot be readily synthesized or purified for screening and testing. If such components were to be tested, they would have to be extracted from the polymer matrix in which they exist. Such an extraction would be a highly complex undertaking, requiring the identification of a long list of parameters such as:

- solvent for the extraction;
- time for the extraction;
- temperature for the extraction;
- surface area of the polymer to be extracted; and
- volume of the extracting solvent.

Varying any of these parameters would affect which polymer components are extracted and how much of any component is extracted. Variation in these parameters can reflect different use conditions of the polymer, different potential exposure conditions, different properties of the polymer, and different components which one desires to extract. In addition, any extraction would yield an extract which is a mixture consisting of the polymer components, primarily the smaller monomer and additive compounds. Thus, any test will yield a result which does not describe the endocrine behavior of the polymer components by themselves. Further, since the conditions of the extraction determine the composition of the extract and the concentration of the components in the extract, the test may not necessarily yield useful information regarding the potential toxicity of the polymer.

Once the polymer components are extracted, the extract may need to be concentrated, for example, to obtain an appropriate concentration for testing or to remove extracting solvents. This “concentration” step must be very carefully conducted so as to ensure that no part of the extract is lost or altered. In most cases, validation of this step would be very difficult.

Migration of Polymer Components

Two types of components are of interest: (1) the lower molecular weight monomers and oligomers that may be present in the matrix of high NAMW polymers; and (2) the additives, catalysts, etc. Because essentially all of these components are on the TSCA Inventory, they will be considered individually along with other chemicals during prioritization and will receive due consideration for screening and testing.

Degradation Products of Polymers

The EDSTAC considered the issue of the potential for polymers to degrade in the environment and therefore pose risk of organismic exposure to substances which would not be captured under the priority setting scheme. Most polymers are chemically designed to be used in applications where stability is essential to their functional and commercial success. Although most polymers would not be expected to degrade in the environment, data are not complete for all polymer classes. However, concern about the ability of chemical degradates to enter the environment, especially water, is not limited to the potential degradates of polymers alone, but includes essentially all chemicals which are released to the environment. The EDSTAC does not consider it necessary to give special consideration to the potential degradates of polymers. These issues will be considered for polymers as well as other chemicals in the priority setting scheme in the context of the exposure criteria.

C. Options Considered by the PSWG

1. Include all Polymers (Regardless of NAMW) From Priority Setting

This option would ensure, in theory, that no molecules are overlooked in priority setting. The polymers would be subject to the same exposure- and effects-related criteria as are the smaller molecules. From a practical standpoint, however, exposure data would be the primary driver in this application, and such data would be hard to obtain for most of the polymers.

For most polymers, the likelihood is small when humans and other animals come in contact with polymers that a significant bioavailable dose would be received. Therefore, the public health value of including all polymers in the prioritization exercise would be negligible. This needs to be balanced in light of the significant resources that would be required to actually characterize the polymeric substance, obtain and evaluate the available exposure and effects data, and make a prioritization decision for thousands of polymers.

2. Include Polymers With NAMW Greater Than 1,000 Daltons to Which Neonates are Likely to be Exposed; Put the Others in Hold

Criteria would need to be developed to identify those polymers which are used in materials most likely to come in contact with neonates. It must be acknowledged that such criteria are most workable for humans and less readily ascertainable for fish and wildlife. Examples of the kinds of polymers that would need to be considered relevant to human neonates include those used in food contact materials, infant toys, etc. A significant advantage of such an effort over option number 1 would be to focus the priority setting on those molecules most likely to present a potential exposure to the sensitive population. The technical difficulties associated with screening and testing polymers, which are described above, would still remain.

3. Hold Polymers With NAMW Greater Than 1,000 Daltons From Priority Setting

No priority setting of the polymer would occur unless data indicate leachable monomers or oligomers have endocrine disruption potential. This option focuses resources on the polymers that contain or might release monomers or oligomers of concern. This still entails a significant technical investment to determine the nature and amount of leachable "other components" from the polymer. Priority setting would initially take place on the monomers under the same criteria as other single chemicals.

4. Exempt all Polymers With NAMW Greater Than 1,000 Daltons; Concentrate on Monomers

This option obviates the resource-intensive step of considering the "other" chemicals present in a typical polymer mixture. Priority setting would take place on the monomers and the appropriate ones would be screened and tested. This is the least resource-intensive option (at the priority setting stage, at least) and focuses on identification of monomers of concern. Concerns about a monomer's use in a polymer arise not during priority setting but after screening and testing is completed. At this point, the results of screens and tests of the monomer, along with the proper dose-response analysis, would be considered with exposure assessment (including use and migration from polymers) to assess risk. This option would still require detailed consideration of polymers, but at a later stage in the program and only for polymers where screening and testing of the monomer and other components indicate a concern.

5. Modified Option 4 – Treat Polymers as Mixtures and Consider Them Along With Other Mixtures

The issues that complicate the consideration of polymers are similar, if not identical, to those faced by mixtures in general. These include often broadly defined composition, wide range of chemicals present in one CASRN (chemical nature and NAMWs), etc. By considering polymers along with mixtures, the consideration of exposure- and effects-related criteria would be similar for both.

D. Recommendation for Handling Polymers

The EDSTAC prefers option number 4. In particular, the EDSTAC recommends that existing and new chemical monomers and oligomers, as well as new chemical polymers with a NAMW of less than 1,000 daltons, should be considered within the broader priority setting scheme and undergo screening and testing as appropriate. The priority setting scheme will consider the potential for sensitive populations to be exposed (e.g., the exposure of neonates). Existing chemical polymers, regardless of NAMW, are viewed as presenting a lower priority for initial action because of the unavailability of critical information such as NAMW and explicit information about the chemical nature of the polymer. In addition, many of the existing polymers are very large molecules (NAMW greater than 50,000 daltons). As such, potential exposure to residual monomers and low molecular weight oligomers contained in existing polymers is limited.

Thus, the EDSTAC recommends:

1. All monomer and oligomer components of polymers should be prioritized for and subjected to endocrine disruptor screening and testing.

2. All "new" polymers (i.e., those produced after the Initial TSCA Inventory, which was published in 1979) with number average molecular weight (NAMW) less than 1,000 daltons should also be prioritized for and subjected to endocrine disruptor screening and testing. Throughout this document, the term "number average molecular weight," or "NAMW," of polymers is utilized. This term indicates a numerical mean, with the actual MW of the polymers ranging about this mean. The EDSTAC recommends embracing the language in the 1995 Final TSCA Polymer Rule (60 FR 16333) which uses a NAMW cutoff of 1,000 daltons, provided that the polymer does not contain other than certain specified reactive functional groups and that the polymer contains less than 10% oligomers with MW less than 500 daltons and less than 25% oligomers with a MW of less than 1,000 daltons.

3. All previously manufactured polymers (regardless of NAMW) and all "new" polymers with a NAMW greater than 1,000 daltons should be set aside pending the outcome of the screening and testing of their monomer and oligomer components.

4. If the component is determined to have endocrine disrupting properties, the component should proceed to hazard assessment.

5. As with any chemical shown to have endocrine disrupting properties, an exposure assessment should be performed. At this stage, all potential exposure routes for a component would be determined, including the potential for the component to be available from the polymer.

Finally, the EDSTAC recommends that EPA gain experience with monomers, oligomers, and new polymers with NAMW less than 1,000 daltons and learn how to apply that experience toward the development of an approach to address existing polymers. This would focus the EDSTP on the polymers about which the best information is available and on those most biologically relevant to the endpoints of concern. To the extent that data generated during implementation of the EDSTP on new chemical polymers indicate a problem, EPA should obtain information on molecular weight, production volume, chemical identity, and any other appropriate information needed to identify and evaluate existing chemical polymers in the priority setting step of the EDSTP. This could be done through the TSCA Inventory Update Rule.

VII. Recommendations for Handling Mixtures

A. Introduction

The EDSTAC has acknowledged the importance of considering mixtures, and public comment at plenary meetings reinforced the Committee's concern over mixtures. This section discusses several of the key issues relating to the screening and testing of chemical mixtures for endocrine disruption and presents: a scheme for organizing the various mixtures, recommended priority setting criteria, and recommendations for initial action.

B. Definition

Quite simply, a mixture is any combination of two or more chemicals. The number of chemical mixtures present in the environment is practically infinite. In addition to the approximately 87,000 chemicals considered for priority setting, many other metabolites, degradates, and combustion products may also occur in the environment. Given this huge array of possible mixtures, the EDSTAC focused on grouping mixtures into general classes.

C. Categorization Scheme for Mixtures

Mixtures can be sorted on where they are found in the environment, their source, and their chemical makeup. The EDSTAC proposes a simple categorization approach to mixtures focused on the range of mixtures found in products, the environment, and human tissues and fluids. The proposed scheme for organizing mixtures, along with examples of categories of data that fit, is outlined below:

1. Products commonly containing mixtures
    a. Pesticide formulations
    b. Cosmetics, toiletries, cleaners, and other consumer products
    c. Petroleum derived products – gasoline, solvents, metalworking fluids
    d. Food – including additives, contaminants, and phytoestrogens

e. Pharmaceuticals/Over-the-counter drugs
f. Other commercial, formulated products

For products commonly containing mixtures, a further three-part distinction can be made between:

- Formulated products – These are products mixed to contain a specified proportion of chemicals necessary for product function. Examples include pesticides, cosmetics, medicines, etc.
- Commercial non-formulated products – These are products which are blended to attain certain performance criteria. In contrast to the formulated products, the proportion of ingredients is generally not fixed. Although knowledge about the precise identity or proportion of the chemicals contained therein is limited, some information about the chemical nature (e.g., aliphatic/aromatic) is available. Examples include fuels, solvents, and lubricants.
- Industrial chemicals – For the purposes of priority setting, these will be considered as single chemicals. However, even though one chemical predominates, other chemical impurities may be present as well. The potential activity of impurities must be considered in the screening and testing of these "single chemicals." Commodity chemicals such as styrene, propylene, and toluene are examples of such "single chemicals."

2. Environmental media commonly containing mixtures (including, but not limited to, TSCA and FIFRA chemicals, metabolites, degradates, and combustion products)

    a. Contaminated media at Superfund sites
    b. Toxic chemicals in urban air
    c. Contaminated drinking water
        i. Pesticides/Fertilizers
        ii. Disinfection byproducts
        iii. Chemicals commonly found in drinking water
    d. Surface water and groundwater
        i. Effluents
    e. Indoor air
    f. Sediments/Sludge
    g. Occupational media (e.g., welding fumes, coke oven emissions, etc.)

3. Tissues and media from humans and other animals (including animals produced for food, fish, and wildlife) commonly containing mixtures (including, but not limited to, TSCA and FIFRA chemicals, metabolites, degradates, and combustion products) from:

    a. Blood
    b. Breast milk
    c. Exhaled breath
    d. Fat

e. Urine
f. Miscellaneous tissues (e.g., finfish, shellfish, meat, poultry, etc.)

D. Determining the Composition of Mixtures to be Considered

Determining the precise composition of mixtures to be considered for prioritization is challenging given the large number of possibilities. This task is somewhat easier for mixtures found in products because the basic formulations are usually well-defined and are not likely to drift widely over time. However, the composition of mixtures found in environmental and biological samples is highly variable with respect to specific components present and their relative amounts. In such cases, higher priority should be given to mixture combinations typically or frequently found in environmental and biological media.

E. Criteria for Prioritizing Mixtures

The following are some recommended criteria for prioritizing mixtures for the purpose of endocrine disruptor screening and testing:

1. Exposure data on mixtures (same criteria as with single chemicals)
   - Biological sampling (human and other biota) data for components of mixtures
   - Environmental, occupational, consumer product, and food-related data
   - Environmental releases
   - Production volume
   - Fate and transport data and models

2. Toxic effects associated with the mixture in question (same criteria as with single chemicals)
   - Toxicological laboratory studies and databases
   - Epidemiological and field studies and databases (populations affected)
   - Predictive biological activity or effects models (e.g., SARs, QSARs)

3. Toxic effects data on major components
   - Use the ranking developed for individual components by the EDSTAC to rank mixtures based on the relative ranking of the components they contain
   - This approach is especially useful for:
     - mixtures for which there are no toxic effects data on the mixture itself. If toxic effects data are available on the mixture, those data should be given primary consideration in priority setting for the mixture.

- environmental contaminants and complex product mixtures, especially if the mixture contains a component with a high priority for screening and testing.

F. Recommendations

The EDSTAC and EPA are, in many ways, entering uncharted territory. The evaluation (including the design, implementation, and interpretation of screens and tests) of the potential for endocrine disruption of *single compounds* is still emerging and fraught with much scientific uncertainty. Nonetheless, the Committee urges EPA to rigorously address the science of mixture toxicology in their research efforts, and recognizes the need, under the auspices of the EDSTP, to begin to confront mixtures.

The science of evaluating mixtures remains complex and unclear for *any* toxic endpoint. Given the potentially overwhelming task of establishing priorities for endocrine disruptor screening and testing of mixtures, the Committee recommends a well-considered, step-wise approach to the inclusion and prioritization of mixtures in the EDSTP. The EDSTAC urges EPA to identify the challenges it faces early in this endeavor, and to address these issues in a transparent fashion.

The recommendations that follow are based on the assumption that, prior to undertaking the T1S step of the program, the following will occur:

- Demonstration/Validation (D/V) of both HTPS and the T1S battery – a limited number of chemicals will be selected and evaluated in the battery of screens recommended by the EDSTAC. The purpose of this D/V phase is to show the utility and validity of the screens to be used in both HTPS and T1S.

- HTPS – a series of transcriptional activation assays will be selected for utilization in the high throughput mode.

Specific recommendations for mixtures:

1. D/V – Include a limited set of mixtures in the D/V phase of screening, including those to be included in HTPS. For the purpose of this phase, a set of mixtures should be selected that spans a range of physical and chemical properties. The goal here is to challenge HTPS and T1S with a variety of chemicals to ensure feasibility and robustness *before* evaluating other mixtures. Clearly, the mixtures chosen for validation may be drawn from mixtures found in the environment and may include "known" endocrine disruptors, but the primary selection criterion should be chemical diversity. This component of the D/V phase is in addition to any D/V efforts done for individual chemicals, as described above.

2. HTPS – If the screens are shown to be capable of handling single components as well as a diverse set of mixtures in the D/V phase, expert judgment (e.g., EDSTAC consensus), guided by a set of prioritization criteria, should be used to evaluate the literature and to decide on a

limited set of mixtures to enter HTPS. Rather than focusing on chemical diversity as in the initial D/V phase, these mixtures should be representative of those found in environmental media or biological tissues. For each mixture, a set of chemicals should be identified that are deemed representative of the chemicals and their proportions found in the selected mixture. The EDSTAC recommended that the PSWG develop prioritization criteria for mixtures and identify a set of mixtures to enter HTPS. These criteria and the set of mixtures are described in Chapter Four, Section VII, E, and Section VII, F, 4, respectively.

3. Screening and Testing – The battery of assays validated for use in the screening program should be used to evaluate the mixtures examined in HTPS. If appropriate, screening should be followed by testing. Additionally, a comprehensive literature evaluation should be undertaken to identify exposure and effects data on mixtures that have not already undergone HTPS. This information should be used to inform the prioritization for Phase II and subsequent phases. During the time it would take to accomplish this, data could be gathered from the screening and testing of single compounds during Phase I and from a limited number of mixtures to help inform the prioritization of other candidate mixtures. The prioritization of mixtures for Phase II and subsequent phases would use the same prioritization criteria as those used for single chemicals.

4. Highest Priority Mixtures for Screening and Testing – The EDSTAC is concerned that the sheer complexity of the mixtures issue could produce "paralysis by analysis" and result in no meaningful progress. To overcome this potential inertia, the EDSTAC urges EPA to focus initially on six types of mixtures. These six types of mixtures have been identified by applying the exposure and effects criteria for priority setting outlined earlier in this chapter. In suggesting that EPA focus its initial attention on these six types of mixtures, by no means does the EDSTAC underestimate the enormous challenge of addressing just these six. However, the EDSTAC believes a systematic approach that focuses initially on these six types of mixtures could shed light on a wide range of technical challenges, help validate screens and tests, and promote development of decision-making protocols for screening and testing other types of mixtures. Thus, the EDSTAC recommends that EPA focus its initial efforts on identifying a relatively small number of representative samples of mixtures (i.e., more than one and fewer than ten) from the following six types of mixtures; and second whether it is technically feasible to run these representative samples through the HTPS, T1S, and T2T. If such steps are determined to be technically feasible, the EDSTAC recommends that the selected representative samples of mixtures be subjected to HTPS, T1S, and, if necessary, T2T. In presenting the six candidate types of mixtures, in several instances the EDSTAC identifies some data sources that EPA might use to initiate the first step of this activity (i.e., to identify a small number of representative samples):

    a) Contaminants in human breast milk – The contaminants in human breast milk are recommended for immediate attention because infants are directly exposed to them. Existing literature demonstrates that human breast milk in the United States and elsewhere is contaminated with a sizable number of chemicals that tend to exist in common proportions (Jensen and Slorach, 1990). Scientific opinion favors breast feeding over reliance on infant formulas and cows' milk in most cases. Therefore, the results of testing

contaminants in human breast milk must be communicated with great sensitivity.

The EDSTAC acknowledges that if hazards are recognized in breast milk, no techniques exist for reducing immediately the hazards to those exposed. But women have a right to know the extent to which they have been exposed to endocrine disrupting chemicals and are entitled to know the hazards to which they are subjecting their infants. Over the long-term, the evidence from analysis of contaminants in breast milk can be an impetus to the evaluation of policies for reducing further exposure to such chemicals.

b) Phytoestrogens in soy-based infant formulas – Soy-based infant formulas contain a complex mixture of plant-derived NONEs – often referred to as "phytoestrogens." In particular, the formulas contain a category of phytoestrogens called isoflavones, specifically genistein and daidzein. But the formulas also contain a wide array of other isoflavones, present as minor components, which also possess estrogenic characteristics (Chapter Four, Section VIII).

c) Mixtures of chemicals most commonly found at hazardous waste sites – ATSDR has published a summary of the combinations of chemicals most commonly found at hazardous waste sites (Johnson and De Rosa, 1995). These mixtures pose a potential hazard to the communities in which these sites are located and, to the extent that such sites are located in lower-income areas, their presence raises issues of environmental justice. Such sites are distributed broadly across the United States.

d) Pesticide/Fertilizer mixtures – Pesticides and fertilizers have commonly been detected in surface water and groundwater across the United States. The National Toxicology Program (NTP) of the National Institute for Environmental Health Sciences (NIEHS) has conducted tests for traditional reproductive and developmental toxicological endpoints of the most commonly occurring mixtures in California and Iowa, two heavily agricultural states (Heindel et al., 1994). Screening and testing these mixtures will provide an opportunity to compare results to the toxicological data already available.

e) Disinfection byproducts – Some of the chemicals used for purifying drinking water supplies produce byproducts that, ironically, may themselves pose a hazard to human health. EPA currently is reviewing monitoring data on disinfection byproducts, with the objective of setting priorities for screening and testing. EPA is whittling down a list of several hundred such byproducts and anticipates, in the short run, NIEHS/NTP initiating testing on approximately ten of these chemicals for carcinogenicity, immunotoxicity, and reproductive effects. Based on whatever results are available from this review and testing, and subject to technical feasibility, the EDSTAC recommends subjecting representative mixtures of the most commonly occurring disinfection byproducts to screening and possible testing for endocrine disruption.

f) Gasoline – Gasoline is a complex mixture of volatile organic compounds to which large numbers of the population are exposed by inhalation. Dermal exposure can also occur, particularly in occupational settings. Subject to technical feasibility, the EDSTAC

recommends that representative samples of this mixture be subjected to screening and, if necessary, testing. The EDSTAC did not have time to identify potential data sources for determining whether it is possible and, if so, what might constitute, representative samples of gasoline.

VIII. Recommendation to Screen Naturally Occurring Non-Steroidal Estrogens

A. Background

Naturally occurring non-steroidal estrogens (NONEs) include natural products derived from plants (phytoestrogens) and fungi (mycotoxins). NONEs are less active than estradiol and diethylstilbestrol (DES) in *in vitro* and *in vivo* assays, but the ubiquitous presence of these compounds in foods indicate that NONEs cannot be ignored (e.g., Cassidy, 1996; Clarke et al., 1996; Gavaler et al., 1995; Sheehan and Medlock, 1995). Moreover, the potential additive, antagonist, and synergistic effects of NONEs with other endogenous and exogenous hormonally active chemical substances are issues that warrant investigation. Significant research on NONEs is being conducted in the United States and other countries to better characterize the benefits and potential hazards (effects) of, as well as the levels of exposure to, these estrogenic compounds.

NONEs are commonly perceived as safe, generally beneficial, and overall innocuous to humans. For example, the low incidence of breast cancer in women within Asia has been attributed to the beneficial effects of the phytoestrogen genistein. Genistein is a major component in soybeans, which comprise a large part of some Asian diets. Moreover, phytoestrogens are recommended as safer, natural alternatives to steroidal estrogens for hormone replacement therapy. However, over the last 40 years, adverse effects of naturally occurring non-steroidal estrogenic compounds have been well-documented in wildlife (range livestock) and laboratory animals. In humans, there are reports that phytoestrogens prolong the menstrual cycle and cause (weak) proliferation of reproductive epithelial cells.

Exposure to NONEs through food sources can occur throughout one's lifetime (i.e., *in utero*, infancy, childhood, and adulthood). Significant quantities of a complex mixture of isoflavone phytoestrogens (predominately genistein and daidzein) are present in various soy-based foods. Soybean infant formulas are widely used in the U.S. and abroad, and there is research under way to determine the effects of these compounds on male infants. Additionally, the exposure and uptake of NONEs in adults is evident because phytoestrogens have also been detected in human breast milk and urine.

The potential effects of NONEs, beneficial and detrimental, should not be dismissed or assumed to be non-existent because organisms have the ability to rapidly metabolize these compounds. Many of the endocrine disruption issues and concerns for pesticides and industrial chemicals may be just as relevant for NONEs. There is substantial evidence to justify a designation of high priority for screening and testing of these compounds based on the exposure to and potential effects of NONEs to both wildlife and human populations. While there is an abundant amount of

in vitro and *in vivo* screening data (mainly uterotrophic and estrogen receptor binding assays) on NONEs, broad-based mechanistic screening and two-generation reproductive/developmental toxicity testing (according to current guideline standards for pesticides and chemicals) is lacking. A review of the literature indicates that:

- Estrogenic plant and fungal natural products are ubiquitous in nature and occur in significant quantities in at least 20 fruits and vegetables including legumes, coffee, beer, wine, and bourbon whiskey and forage clover. (Cassidy, 1996; Clarke et al., 1996; Gavaler et al., 1995; Richard and Thompson, 1997; Thomas, 1998; Verdeal and Ryan, 1979; Wiese and Kelce, 1997).
- NONE levels vastly exceed pesticide residues in food. The typical daily intake of isoflavones by humans, estimated to be 0.6 mg/kg/day, can prolong a human female's menstrual cycle. The daily intake of a vegetarian who consumes very large quantities of soy-derived nutrients could be much higher. (Adams, 1996; Cassidy, 1996; Clarke et al., 1996; Wiese and Kelce, 1997).
- Coumesterol is uterotrophic in female rats fed over a 90-hour period at dose levels within the range reported in human foods. Exposure of newborn rats to 100 ug/day of coumesterol accelerates the onset of puberty, increases the incidence of persistent vaginal keratinisation and induces bloody ovarian follicles. (Clarke, 1996; Sheehan and Medlock, 1995; Verdeal and Ryan, 1979; Wiese and Kelce, 1997).
- The deleterious effects of clover phytoestrogens on grazing sheep is well-documented. Effects range from temporary and permanent infertility to permanent abnormalities in their reproductive organs. (Adams, 1996; Thomas, 1997; Verdeal and Ryan, 1979).
- At doses up to 50 mg/day by oral administration, zearalenone, a corn mycotoxin, produces effects on the vulva, uterus, ovary, cervix, and mammary glands of swine. Sows receiving 5 mg of purified zearalenone daily throughout the last month of pregnancy produced litters with stillborn pigs or pigs with a "splayleg" incoordination of hind limbs. (Adams, 1996; Wiese and Kelce, 1997; Verdeal and Ryan, 1979).
- Phytoestrogens (genistein) can be both tumor promoters and inhibitors depending on the target organ and the dose. Genistein has been observed to inhibit both tyrosine kinase and topoisomerase II. The latter is the target site of action for taxol, a drug currently used to treat breast cancer. (Clarke et al., 1996; Lien and Lien, 1996; Markovits, 1989).
- NONEs may produce various biological responses *in vivo*. NONEs may act as estrogen agonists or antagonists (anti-estrogenic effects). These effects could either be beneficial or deleterious depending on the target tissue and dose. Additionally, NONEs may cause other responses through other mechanisms that do not involve the estrogen receptor, for example genistein. Additionally, it is reported that some phytoestrogens may alter the concentration of sex-hormone-bonding globulin which, in turn, alters the bioavailability of endogenous hormones. (Adams, 1996; Cassidy, 1996; Clarke et al., 1996; Safe and Gaido, 1998; Sheehan and Medlock, 1995; Wiese and Kelce, 1997; Wiseman, 1996).

B. Recommendation

The EDSTAC therefore recommends screening and, if necessary, testing: (1) representative

NONEs singularly; and (2) a complex mixture of NONEs (e.g., soy-based infant formulas as discussed in Section VII of this chapter). Data from the representative compounds should be compared to hormones and synthetic chemicals. The representative compounds should come from the major chemical classes of estrogenic natural products. Testing soy-based infant formulas should be made part of the initial investigation to evaluate mixtures.

The following NONEs were chosen from the literature based on their reported effects (beneficial and deleterious) to wildlife and/or humans and on their widespread occurrence in nature. These NONEs should be screened and, if necessary, tested.

Representative NONEs:
1. Isoflavones: genistein, daidzein, miroestrol, biochanin A, formononetin, equol
2. Flavones: kaemferol, naringenin
3. Coumestans: coumesterol
4. Dihydrochalcones: phoretin
5. Triterpenes: betulafolienetriol (ginseng)
6. Lignans: enterolactone

Representative estrogenic mycotoxin:
7. Beta-resorcyclic lactones: zearalenone, zearalenol, zearanol

IX. Recommendation for a Nominations Process

A. Introduction

The EDSTAC recommends that EPA establish a process that would allow affected citizens to nominate chemical substances or mixtures for endocrine disruptor screening and testing. In general, the nominations process recommended by the EDSTAC is intended to focus on chemical substances or mixtures where exposures are disproportionately experienced by identifiable groups, communities, or ecosystems rather than on chemical substances or mixtures where exposures are more broadly experienced by the general population at the regional and/or national levels. As such, the nominations process is intended to provide a mechanism for prioritizing chemical substances or mixtures that are unlikely to be considered as high priority through the core priority setting process. For this reason, the EDSTAC recommends that the nominations process should run parallel to, but be separate and distinct from, the core priority setting process described earlier in this chapter.

B. Description of the Nominations Process

Consistent with the overall philosophy of the core priority setting process, as described in Section XI of this chapter, chemical substances and mixtures that are nominated will, in effect, be placed in one of the "compartments" of the overall compartment-based approach to priority setting (Chapter Four, Section XI). The EDSTAC recommends a goal for each phase of the EDSTP of no less than 5% of the total number of chemical substances or mixtures subjected to T1S drawn from substances receiving nominations but not selected through the main priority setting process. The EDSTAC recognizes that the total number of nominations or their quality may be such that this goal cannot be met in specific phases. For each phase of the EDSTP, the nominated chemicals should be evaluated against the specialized criteria described below. Priorities for the nominated chemicals should be established in accordance with these specialized criteria on a separate track, rather than attempting to integrate the prioritization of the nominated chemicals with the chemicals that are selected for T1S through the core priority setting process. Any nominated chemical substance or mixture that becomes a priority for T1S through the core priority setting process should be removed from consideration within the list of nominated chemicals in order to ensure that the priorities drawn from the nominations process will compete only against other nominated chemicals.

The nominations process should allow for an early opportunity to submit nominations during each phase of the EDSTP. A call for nominations should be made via a public notice specifying both the criteria by which nominations will be evaluated and the deadline for submitting nominations. The time period for submitting nominations should end prior to the expected Federal Register (FR) notice announcing EPA's formal proposal for T1S priorities. As a part of the public comment period following such an announcement, members of the public should be given an opportunity to comment on all chemicals that are proposed for T1S. Chemicals not included in the priority list for each phase of the EDSTP could be nominated at the start of the next phase. However, the public comment period following the FR notice should not be considered a second opportunity to nominate chemicals for the current phase of the program.

C. Criteria for Evaluating Nominated Chemicals

As noted above, the EDSTAC recommends that the nominations process should utilize a different set of criteria than will be used for the core priority setting steps of the EDSTP, particularly with respect to exposure. The exposure-related criteria for the nominations process should be designed to allow for chemical substances and mixtures for which there may not be widespread exposures on a national scale, but for which there are exposures on a smaller scale, to be eligible to receive a priority status for T1S. Thus, the nominations process should be designed to focus on exposures that are disproportionately experienced by identifiable groups, communities, or ecosystems.

After exposure-related criteria have been considered in the evaluation of nominated chemical substances and mixtures, it is likely that effects-related information will need to be considered to help further set priorities among nominations. This is potentially problematic because there is likely to be a lack of effects-related information. In fact, the lack of effects data may be the very reason for public concern. That is, communities may be regularly exposed to a chemical substance or mixture that has not undergone meaningful toxicological evaluation. Nevertheless, if there are effects data, or if the chemical substance or mixture is chemically similar to another chemical substance or mixture for which effects data are available, the Committee recommends that EPA utilize those data as a secondary source of information to help set priorities among nominees.

In summary, when evaluating nominations, EPA should consider nominated chemical substances and mixtures that meet the following criteria to be a higher priority than those that do not meet these criteria:

- chemical substances and mixtures for which there is a likelihood of a regularly completed exposure pathway as compared to chemical substances and mixtures for which the exposure pathway is likely to be completed only rarely or occasionally;
- chemical substances and mixtures that affect a high proportion of people within a given community or workplace; and
- chemical substances and mixtures for which there may be direct or indirect (i.e., model derived) effects-related data regarding the endocrine disrupting potential of the nominated chemical substance or mixture.

D. Submission of Nominations

Members of the public should be encouraged to submit nominations with as much information as possible, but it should still be permissible to do so without data or evidence as it relates to the specialized criteria. Lack of such information should not preclude EPA from evaluating a nominated chemical on par with nominated chemicals for which data have been submitted. EPA should make use of all information available to the Agency, including anecdotal information that may be submitted, as well as information gathered as part of the core priority setting process (e.g., information contained within the EDPSD recommended in Section X of this chapter). Recognizing that the nominations process may be vulnerable to misuse for various reasons, the EDSTAC recommends that the Agency design a nominations process that protects nominators, workers, communities, registrants, manufacturers, etc., as appropriate. Recognizing that misuse could significantly detract from its intended purpose, the EDSTAC recommends that the nominations process be as transparent as possible and that EPA provide the list of nominations with any appropriate supporting information in appropriate publications, such as the Federal Register Notice and/or the Internet.

The identity of nominating organizations should be made public. The identity of individual nominators should be kept confidential by EPA upon written request. In order to assist EPA in its evaluation of nominated chemicals, the Committee recommends that nominations should include

the following types of information:

- how exposure to the nominated chemical substance or mixture may be disproportionately experienced by identifiable groups, communities, or ecosystems;
- the reasons for the nomination (which may include both exposure- and effects-related concerns) and any information that provides a basis for those concerns; and
- the degree of support for the nomination from the potentially affected communities and/or workplaces.

E. Mixtures in the Context of the Nominations Process

The EDSTAC expects nominations of chemical mixtures as well as individual chemical substances. However, as with the broader discussion of mixtures contained in Section VII of this chapter, the EDSTAC recognizes there are difficult technical and policy issues surrounding the issue of screening and testing mixtures. The EDSTAC is particularly concerned that EPA and other governmental agencies, in anticipation of the nominations process raising expectations for action, be prepared to take whatever steps may be appropriate to address potential public health and environmental impacts that are identified through the EDSTP. Similarly, the EDSTAC recommends that the communication and outreach effort that will accompany the nominations process should address the capabilities, as well as the limitations, which EPA and other governmental agencies are likely to face in any effort subsequent to the screening and testing stage of the process.

F. Ability to Track Nominations

As recommended in Chapter Six of this report, members of the public should be able to track and locate the progress of all chemicals in the EDSTP through a centralized, on-line database run by EPA. This on-line database will provide an opportunity, in addition to the FR notice, for members of the public to determine the status of chemicals that may be of concern to them.

X. The Endocrine Disruptor Priority Setting Database

A. Introduction

As described in other sections of this chapter, the PSWG began its work by describing exposure- and effects-related information categories and criteria to be used for sorting and prioritizing chemicals for endocrine disruptor screening and testing. The PSWG also identified and evaluated data sources associated with these categories and criteria. These data sources are listed in matrices contained in Appendix G.

After identifying these data sources, the PSWG grappled with how to use them to sort and

prioritize chemicals for endocrine disruptor screening and testing. Over time it became clear that there was much value and utility in assembling the relevant and useful data sources into a single relational database, which is referred to as the Endocrine Disruptor Priority Setting Database (EDPSD). The PSWG had contemplated developing and using the EDPSD to assist in the EDSTAC's deliberations and, in particular, to help the work group and the Committee understand the implications of alternative approaches to priority setting. After making significant progress on the prototype EDPSD, the PSWG and the EDSTAC came to realize that the tool could not be completed given time and resource constraints.

This section presents recommendations on the further development, utilization, and maintenance of the prototype EDPSD. The recommended approach to priority setting contained in Section XI of this chapter builds upon the recommendations contained in this section.

B. Recommendation and Principles to Guide the Continued Development, Utilization, and Maintenance of the Prototype EDPSD

The EDSTAC recommends that EPA continue to develop and maintain the EDPSD as a tool that can be used to expeditiously sort and prioritize chemicals for endocrine disruptor screening and testing. The EDSTAC identified several principles that should guide EPA's use of the EDPSD, along with the process EPA should follow in conjunction with use of the EDPSD.

Most importantly, the EDPSD itself, as well as the process by which it is utilized, should be open and transparent. As described in more detail below, EPA should convene a multi-stakeholder group prior to the completion of the tool. This group would serve to help ensure that the tool was developed and ultimately used according to the guidelines suggested by the EDSTAC. EPA and the multi-stakeholder group should develop ground rules to prevent the use of the EDPSD to confirm *a priori* assumptions regarding the priority for screening specific chemicals or as a means to hide or obfuscate the basis for priority setting decisions. Furthermore, EPA should provide notice and opportunity to comment on the proposed database tool before it is used by the Agency. This will allow an opportunity for additional chemical-specific data that might not otherwise be included in the identified data sources to be incorporated into the EDPSD.

C. Description of the Prototype EDPSD

The prototype EDPSD is a relational database that (as of December 1997) contains records for approximately 87,000 chemicals with Chemical Abstracts Service Registry Numbers (CASRNs) from data sources related to the information categories and criteria described in Sections III and IV of this document. It was created using Molecular Design Limited Information Systems' Integrated Scientific Information System. The CASRNs of discrete organic chemicals, polymers, and inorganic chemicals from each data source were entered in a multi-field format. The number of chemical records in the EDPSD is determined by the cumulative number of chemical records contained in each data field.

The data fields included in the prototype EDPSD were used to develop a form that appears on the computer screen during operation of the EDPSD (Figure 4.2). When queried using particular scenarios (e.g., how many TRI chemicals produced between 10,000 and one million pounds appear in Great Lakes fish (GLC Fish) and also occur in the ATSDR database, etc.), the EDPSD provides the number of chemicals meeting the criteria used. Any number of scenarios can be developed depending upon user interests. The prototype EDPSD showed great promise in providing numbers of chemicals that displayed certain criteria, and also has potential to develop algorithms combining different criteria. However, early queries using different scenarios occasionally resulted in numbers that were known to be inaccurate. It was assumed that the inaccuracies were resolvable by adequately cross-referencing the different data fields and conducting appropriate QA/QC corrections to the data included in the fields. However, the QA/QC exercise could not be completed in the tight time frame of the EDSTAC schedule. As such, final development, demonstration, and validation of the EDPSD was viewed as a high priority, post-EDSTAC task for EPA with multi-stakeholder involvement. A more detailed description of the EDPSD follows.

All data fields in the EDPSD (Figure 4.2, Tables 4.1, and 4.2) are linked by CASRNs, and there are no duplicate records for any chemical. For most discrete organic chemicals, chemical formulas, molecular weights, and Simplified Molecular Input Line Entry System (SMILES) notations and chemical structures were entered into the EDPSD.

There are two types of fields in the EDPSD – logical and numerical. Logical fields are binary in nature (i.e., +/-, yes/no, true/false, etc.). For example, a chemical either is present or absent in a particular data source that is included in the EDPSD. Numerical fields, by contrast, are quantitative. They provide an actual measured value or, alternatively, an estimated number associated with a particular data source or environmental fate parameter (e.g., an estimated hydrolysis half-life of two hours).

As a relational database, the EDPSD may be queried in a wide variety of ways to answer questions in minutes that would otherwise take hours, days, or weeks to answer. As noted earlier, the EDPSD can be used to rapidly estimate the numbers and types of chemicals in different data sources that meet different criteria (e.g., the number of chemicals with annual production/importation volumes greater than one million pounds per year and log octanol water partition coefficients (LogP) > 6 that are measured in Great Lakes fish and identified by California's Proposition 65 as reproductive toxicants).

The EDPSD is a very powerful tool for exploring alternative approaches to the application of the criteria described in Sections III and IV in this document. As described more fully in Chapter Four, Section X, G, the EDSTAC recommends that EPA and the multi-stakeholder group make full use of the EDPSD in an effort to advise the Agency on its final decisions for priority setting for T1S. However, the EDSTAC recommends that EPA and the multi-stakeholder group not be

limited to data that can easily be placed into a database format such as the EDPSD when providing advice and making final decisions on priorities for T1S (Chapter Four, Section X, E).

D. Preliminary Recommendation for Data Fields to be Included in the EDPSD

As noted above, significant progress was made in developing the EDPSD, but the tool was not completed given the time period and resources available to the EDSTAC. During the course of its work, the PSWG spent time grappling with the question of what data sources should be considered for inclusion in the EDPSD. This section outlines some of the PSWG's preliminary conclusions, which should be a starting point for the recommended development and implementation of the EDPSD to be completed by EPA and the proposed multi-stakeholder group. The following data sources should be included, but are not considered to comprise a final comprehensive list. Rather, they illustrate the kinds of data sources that might be included in the final version of the EDPSD. The data field examples (Figure 4.2, Tables 4.1, and 4.2) are categorized by type, and each data field example is further described in Appendix G.

E. Special Handling of Effects Data in the Context of the EDPSD

The proposed EDPSD is a relational database tool that the EDSTAC recommends be used to assist in prioritizing chemicals for endocrine disruptor screening and testing. The prototype EDPSD has purposely been designed to be user-friendly, transparent, and flexible. However, these very qualities make it difficult, if not impossible, to include information from the general scientific literature that is not organized into accessible numerical or logical databases. Though this represents a significant shortcoming, the EDSTAC believes the EDPSD is sufficiently versatile to justify its use. However, the EDPSD should not be used in isolation from other "tools," nor should it be used to perform functions that do not lend themselves to its design.

There are numerous data sources that provide toxicological, epidemiological, or field study data that may be useful in prioritizing chemicals for endocrine disruptor screening and testing. Although far from comprehensive, published studies can be identified through widely available scientific literature databases such as Medline, Toxline, and NIOSHTIC.

Substance-specific reports are also widely available that include summarized data reviewed by the authors. Such reports are prepared by various organizations and agencies such as the International Agency for Research on Cancer (IARC), NIOSH (Criteria Documents), ATSDR (Toxicologic Profiles), to name a few. Other sources of compiled data exist in the substance-specific rules and rule-making dockets of regulatory agencies such as OSHA, EPA, CPSC, or on-line data summaries such as the EPA IRIS system. Less exhaustive reviews are also found in agency investigative reports such as the NIOSH Health Hazard Evaluation reports or ATSDR hazardous site evaluations. Research grant progress and final reports submitted to NIH, EPA, private foundations, etc., on the other hand, are not widely available. Lastly, some companies

Figure 4.2. Example of data fields arranged into a form as they might appear on a computer screen

CASRN	MW	Formula	Name
SMILES			

Exposure-Related Criteria:

Biological Sampling

NHATS

Environmental Sampling

Invertebrates, Fish, and Wildlife	GLC Fish	ATSDR/PL

Release to the Environment

TRI

Chemical Production or Importation

< 10,000 lbs.	> 10,000 < million lbs.	> million < billion lbs.	> billion lbs.

Site-limited intermediates	Polymers	Inorganics

Fate and Transport

LogP	Hydrolysis half-life (d)	Atmospheric (OH radical) half-life (d)	HLC (atm/cum /mole)	VP (mm/Hg)	Water solubility (mg/l)	K_{OC}	BCF

Effects-Related Criteria:

Laboratory Studies

RTECS	TSCATS 8(e) HE RTOX	TSCATS 8(e) EE RTOX	Prop 65

Predicted Biological Activity/Effect
Epidemiology/Field Studies

ER QSAR

Statutory-Related Criteria:

FQPA

Active Ingredients	Inert Ingredients

SDWA

SDWA CCL

Table 4.1. Existing files (and field type) in the Endocrine Disruptor Priority Setting Database

More information on the existing and proposed data fields recommended for inclusion in the EDPSD may be found in Appendix G of this report.

Generic and Notation Files:

1. **Descriptive** (all textual) – CASRN, Chemical name, Chemical formula, and SMILES
2. **Quantitative** (numerical) – Molecular weight

Exposure-Related Criteria Files:

1. **Biological Sampling Data** (logical) – NHATS*
2. **Environmental, Occupational, Food, and Consumer Product Data** (logical) – Great Lakes Fish, Invertebrates, Fish, and Wildlife, ATSDR/PL
3. **Environmental Release Data** (logical) – Toxics Release Inventory*
4. **Production/Importation Volume Data** (logical) – Annual production volume categories* for discrete organic chemicals ($x \leq 10{,}000$ lbs.; $10{,}000 \leq x \leq 1{,}000{,}000$ lbs.; $1{,}000{,}000 \leq x \leq 1{,}000{,}000{,}000$ lbs.; $x > 1{,}000{,}000{,}000$); Site-limited intermediates, Polymers, and Inorganics
5. **Fate and Transport Data and Models** (all numerical) – Estimated LogP (based on QSARs); Hydrolysis half-life, Atmospheric half-life, Henry's Law Constant, Vapor pressure, K_{OC}, Water solubility, and Bioconcentration factor

Effects-Related Criteria Files:

1. **Toxicology Laboratory Studies & Epidemiology and Field Studies and Databases** (all logical) – RTECS, TSCATS 8(e), HE RTOX, EE RTOX, and Proposition 65
2. **Predictive Biological Activity or Effects Models** (numerical) – Hologram QSAR for estrogen receptor binding

Statutory-Related Criteria Files:

1. **FQPA** (logical) – Pesticide active ingredients, Inerts*
2. **SDWA** (logical) – Contaminant Candidate List*

(*****) Indicates data files that are currently logical, but could be changed to numerical with appropriate quality control and analysis.

Table 4.2. Examples of file types that could be placed in the Endocrine Disruptor Priority Setting Database

Exposure-Related Criteria Files:

1. **Biological Sampling Data** – NHANES, TEAM, NHEXAS (when available)
2. **Environmental, Occupational, Consumer Product, and Food-Related Data** – Published data on measured concentrations of industrial chemicals, pesticide active ingredients and inerts in air, drinking water, ground water, surface water, sediment, and soil (e.g., ACGIH/TLV, FDA/GRAS, OSHA/PEL, FDA/PAFA)
3. **Environmental Release Data** (logical or numerical) – ATSDR/HSEES (logical numerical), USGS Pesticide Monitoring Program
4. **Production/Importation Volume Data** (logical or numerical) – Non-CBI individual production volumes for industrial chemicals, discrete organic chemicals, polymers, inorganics, pesticide active ingredients, and inerts
5. **Fate and Transport Data and Models** (all numerical) – Measured data for LogP, Hydrolysis half-life, Atmospheric half-life, Henry's Law Constant, Vapor pressure, K_{OC}, Water solubility, and Bioconcentration factor, Estimated and measured biodegradation rate data

Effects-Related Criteria Files:

1. **Laboratory Toxicology Studies & Epidemiology and Field Studies and Databases*** (all logical) – RTECS, TSCATS 8(e), HE RTOX, EE RTOX, and Proposition 65
2. **Predictive Biological Activity or Effects Models** (numerical) – Hologram QSAR for estrogen receptor binding

Statutory-Related Criteria Files:

1. **FQPA** (logical) – Pesticide active ingredients and inerts*
2. **SDWA** (logical) – Contaminant Candidate List*

(*****) Indicates data files that are currently logical, but could be changed to numerical with appropriate quality control and analysis.

maintain published literature databases relevant to their products as well as epidemiological data on the health experience of their work force. Unfortunately, for any given chemical substance or mixture, the process of collecting and assessing most of these data is extraordinarily time consuming and resource intensive.

For these reasons, the EDSTAC recommends that EPA make use of the potentially valuable information contained in the scientific literature in an efficient and cost-effective manner. In particular, EPA should make use of all of the data that is available to it in a step-wise fashion, starting first with data that lends itself for inclusion in the EDPSD. This will include data from databases such as RTECS and TSCATS, which are limited to positive findings from the literature. Other databases that contain abstracts of studies but are not limited to positive findings could be searched next for those chemicals that either have positive findings in RTECS or TSCATS or that warrant further review due to the application of other effects-related information or criteria (e.g., positive HTPS or QSAR results). Finally, if necessary and helpful to the process of either making or justifying the basis for final priority setting decisions, EPA could review the literature available on a particular chemical.

F. Continued Development of the EDPSD

In order to complete data collection in anticipation of the use of the EDPSD, data from additional files need to be included in the database, and the relevance of those files to priority setting for endocrine disruptor screening and testing needs to be provided as part of the justification for their addition. All new chemicals from each additional file must include, at a minimum, CASRNs and molecular weights. All new discrete organic chemicals from each additional file must also include SMILES notations and chemical structures.

The EDSTAC recommends that EPA provide resources to complete the QA/QC investigations of files that are currently in the EDPSD. The EDSTAC further recommends that EPA provide resources to add new files to the EDPSD in stages. These files and the stages for their addition could include:

1st stage: EPA and other databases that provide data on use for industrial chemicals and pesticides; information from pesticide ecotoxicity, fate, and toxicity one-liners; chemicals that are non-food-use pesticide active ingredients and non-food-use other pesticide ingredients; chemicals on the Generally Regarded As Safe (GRAS) list; and chemicals in the Priority Assessment of Food Additives (PAFA) database.

2nd stage: Data on chemical use that were not readily available in databases; chemicals and concentrations of chemicals in National Health and Nutrition Examination Survey (NHANES), Total Exposure Assessment Methodology (TEAM), and ATSDR's Hazardous Substances Emergency Events Surveillance (HSEES) files; measured chemical fate data; and additional QSARs for endocrine disruptors.

3rd stage: Inclusion of HTPS data and improved QSARs.

The EDSTAC recognizes that the time and resources required to add new files will depend upon a

number of factors, including: when pending files are received, the format of received files, the determination of whether to use files as sources of numerical or logical data, conversion of logical files to numerical files, completion of QA/QC investigations of the files and data, and expediency of the input process.

G. Use by Multi-Stakeholder Group

The EPA should convene a multi-stakeholder group prior to completion of the tool. This group would serve to ensure that the tool was developed and ultimately used according to the guidelines provided by the EDSTAC. This multi-stakeholder group should provide input and assistance to EPA in completing the development of this tool. Once the tool is completed, the multi-stakeholder group should be provided an opportunity to make use of the tool to provide input on the priorities for T1S. However, EPA would ultimately be responsible for setting priorities for T1S. Presumably, the group would follow the approach to priority setting recommended in Section XI of this chapter. Specifically, the group should make use of the EDPSD to understand the implications of its recommendations to EPA regarding the number and types of chemicals that should be included on the list of priority chemicals for T1S in Phase I of the program.

The EDSTAC recommends that the multi-stakeholder group convened for this purpose be approximately half the size of the EDSTAC, but with the same degree of balance and diversity of interests. EPA should establish ground rules for the multi-stakeholder group that encourage the group to stay focused on the development of a fair and scientifically sound set of final recommendations of priorities for T1S. As indicated earlier, the ground rules should encourage the assembled group not to use the EDPSD as a tool that simply confirms or justifies a set of *a priori* assumptions.

Finally, the EDSTAC recommends that the Agency provide an opportunity for public comment on the content and structure of the database tool, as well as on the approach or way in which the Agency intends to use the tool. Among other things, this will allow an opportunity for submission of additional chemical-specific data to be incorporated into the database tool. The EDSTAC also recommends that, after receiving comment on the tool itself, EPA propose for public comment its T1S priorities.

H. Maintenance

In order for the EDPSD to remain a timely and viable tool, the EDSTAC recommends that EPA update the database every six months at a minimum, and more frequently if time and resources permit. If maintained properly, the EDSTAC believes the tool will not only provide the capability to understand the "real-world" implications of alternative approaches to priority setting, but the tool will also have broad application and pertinence, once knowledge of the existence of the tool spreads.

XI. Recommended Approach to Priority Setting

A. Introduction

The EDSTAC's recommended approach to priority setting establishes an initial sorting step to separate the universe of chemicals that need to be considered for endocrine disruptor screening and testing into four distinct categories:

1. polymers that will be placed into a "hold" status (with some exceptions) pending a review of their monomers and oligomers;
2. chemicals for which there are insufficient data to proceed to either T2T or hazard assessment and will therefore need to be prioritized for T1S;
3. chemicals for which sufficient data exists to go to T2T; and
4. chemicals for which sufficient data exists to go to hazard assessment.

In this concluding section of the Priority Setting chapter, a number of issues are presented which the PSWG considered in developing its recommendations, followed by the EDSTAC's recommended approach to setting priorities for T1S. Also included is the EDSTAC's rationale for its recommendation to rely on EPA's schedule for tolerance reassessments under the FQPA as the basis for setting priorities for food-use pesticides that will be permitted to bypass T1S and go directly to T2T.

B. Obstacles to an Ideal Priority Setting System

In an ideal world, EPA would have sufficient information on exposures to and effects from candidate chemicals to provide a basis for priority setting. In reality, existing data sets are uneven in quality and quantity. The EDSTAC's review of available data, contained in Sections III and IV of this chapter and in Appendix G, attests to these problems. Major characteristics of this unevenness include the following:

- Many more data are available on the effects of the relatively small number of active ingredients in pesticides (approximately 900) than on the thousands of industrial chemicals

produced in much larger quantities.

- Biological monitoring data for humans are scarce. A relatively small number of chemicals (on the order of 100 or less) have been routinely sampled in human blood and urine in the United States, and the major U.S. national program for sampling concentrations in human tissues was discontinued in 1990.
- Monitoring data for other organisms, while more numerous than human data, still focus on a relatively small number of chemicals.
- Data on routine chemical releases to the environment, while markedly better than they were prior to the creation of the Toxic Release Inventory about 10 years ago, still encompass only 528 industrial chemicals and pesticides and frequently rely on engineering estimates rather than on actual releases.

C. Principles for Setting Priorities

The EDSTAC's report could have been designed primarily to assist EPA in implementing the screening program provisions of the FQPA and the SDWA. But, as noted earlier, the EDSTAC saw its charge as reaching beyond these specific statutes and EPA's regulatory authority. The EDSTAC acknowledges that EPA's implementation of these priority setting recommendations will be influenced most heavily by its statutory authorities. Nevertheless, the EDSTAC hopes its broad, scientifically derived approach will encourage voluntary testing behavior within the private sector and new screening and testing initiatives by other agencies.

The proposed priority setting system for T1S is based on the following three principles:

1. The system should be "transparent."

   Environmental health concerns in the United States are usually addressed in decisions that represent a mix of scientific judgment and individual and shared values. Priority setting for endocrine active chemicals is especially value-laden, because necessary knowledge of effects and exposures is so lacking. There are many different, reasonable, and not obviously wrong ways of deciding how to apply the information categories and criteria identified by the EDSTAC. The manner in which these are used should identify as clearly as possible the weights assigned to various categories and the rationales underlying those weights.

2. The system should reflect guiding principles derived from the EDSTAC's review of existing data on effects and exposures.

   Sections III and IV of this chapter present the EDSTAC's major conclusions about the strengths and limitations of the information included in each exposure- and effects-related information category, as well as on a set of guiding principles for how to use the information in setting priorities. These guiding principles are principles for weighting data. A nonexhaustive list includes, for example:

- The greater the relevance of a biological sampling data set to large populations, disproportionately exposed subpopulations, or particularly susceptible subpopulations, the more weight the data set should be given.
- The more likely a chemical is to be internalized by an organism from its environment, the greater weight it should be given.
- The more likely environmental releases are to lead to organism exposure, the greater weight the release data should be given.
- Production volume should not be used to prioritize between existing industrial chemicals and pesticides, because production volumes for high-volume industrial chemicals are several orders of magnitude higher than those for pesticides.

3. The system should rely heavily on empirical data, but the highest priority should not be assigned solely to those chemicals for which the most empirical information on exposures and effects has been gathered.

   The most solid evidence of exposures comes from monitoring of organisms, including humans. Chemicals detected in organisms should be weighted heavily in the priority setting system. However, the number of chemicals monitored in this fashion is limited. Therefore, chemicals that may not be widely monitored in organisms or environmental media, yet are of potential concern, should not be excluded completely from the highest priority rankings. Existing empirical data on selected chemicals can and should be used to improve the predictive capacity of models for chemicals lacking empirical data.

   The EDSTAC also prefers weighting heavily empirical evidence of effects, at least until it is learned how to develop better models for use in the assessment process. The EDSTAC recognizes that there is a risk that heavily weighting those chemicals about which the most is known may penalize those chemical producers who have evaluated the potential effects of their products. The Committee acknowledges this possibility, but it should be kept in perspective. It applies mainly to active ingredients in pesticides. Since the food-use pesticides (approximately 500 of almost 900 currently registered active ingredients) may go directly to T2T anyway, thereby skipping T1S, the availability of large amounts of data on these pesticides will not raise their priority for T1S higher.

D. Recommended Strategy for Setting Priorities for Tier 1 Screening

The EDSTAC advocates adoption of a "compartment-based priority setting strategy." This strategy builds directly upon the several distinct exposure- and effects-related information categories and criteria found in Sections III and IV, respectively, as well as several specially targeted priorities identified elsewhere in this chapter, including: mixtures (Section VII), naturally occurring non-steroidal estrogens (Section VIII), and nominations (Section IX). The basic premise of a compartment-based priority setting strategy is to establish separate priorities for a limited number of separate compartments. The term "compartment" simply refers to the particular information category or criterion or combinations of information categories or criteria that define each set of priorities. Such compartments can be defined by the integration of

exposure and effects data, the consideration of exposure data on their own, effects data on their own, or specially targeted priorities, as described below.

A compartment-based approach can be contrasted with approaches that strive to develop a single rank-ordered priority list that integrates all exposure- and effects-related information categories and criteria. The Committee believes the proposed compartmentalized approach best accommodates its principles for priority setting and the real-world situation of uneven data.

E. Examples of Compartments for the Recommended Priority Setting Strategy

While the EDSTAC endorses the general framework of a "compartment-based priority setting strategy," the specific compartments and the weights and/or order in which they should be utilized have not yet been agreed upon. Thus, the compartments described immediately below are intended solely as examples.

Where the EDSTAC was confident of the data that are pertinent to a particular compartment, the number of chemicals estimated to fall within each compartment are indicated below. For some of the example compartments, the EDSTAC did not have sufficient data to provide estimates. The compartments are *not* listed in order of agreed-upon priority.

As noted above, the following *examples* of compartments fall within four major categories:

- Integrated Exposure/Effects – Each of these compartments draws first from databases containing information on exposures. Within each compartment, priorities are set on the basis of effects data. *For purposes of illustration only*, these data on effects are presumed to come from TSCATS, RTECS, HTPS, and QSAR models. These are the databases currently projected for inclusion in the EDPSD. Elsewhere in this chapter, the challenge of readily assessing effects data, and the desirability of taking a "tiered approach" to such assessments that goes more deeply into or beyond databases such as those mentioned specifically above are described. It is anticipated that most of the chemicals in Phase I will be prioritized based on integrated exposure and effects data.

- Exposure Only – Compartments in this category would prioritize chemicals based on exposure data only, without using effects data. It is anticipated that chemicals in these compartments would be relatively few compared to those taken from integrated compartments. These compartments would focus on identifying chemicals with high production volumes. Special attention should be paid to chemicals for which there is evidence of embryonic, *post partum* or post hatch, early life stage, and pre-maturation exposures.

- Effects Only – Compartments in this category would prioritize chemicals based on effects data only, without using exposure data. It is anticipated that chemicals prioritized in these compartments taken for screening in any one phase would be relatively few compared to those taken from integrated compartments. These compartments would focus on identifying chemicals with noteworthy effects data.

- Specially Targeted Categories – These categories – which presume widespread exposure and the possibility of widespread effects – include mixtures, nominations, and non-steroidal estrogens. The nominations category can include less widespread, yet elevated exposures and can be driven by reported effects that might be associated with exposures to chemicals.

1. *Examples* of Integrated Exposure/Effects Compartments

   a) Chemicals found in human biological samples

      These are the most solid indicators of human exposure. They number approximately 100 chemicals and include chemicals from the NHATS, NHANES, and TEAM studies described earlier in this chapter and in Appendix G, Table 1. Some of these substances may bypass T1S and go directly to T2T. Priorities for screening among the remaining substances can be established based on effects data, with the highest priority given to chemicals on this list for which there is some indication of possible biological effects. The EDSTAC acknowledges that some of the human sampling data are not current, but believes they are nevertheless worthwhile to use.

   b) Chemicals found in wildlife samples

      These are the most solid indicators of wildlife exposure. U.S. Fish and Wildlife Service's Environmental Contaminant Data Management System lists 625 compounds and the Great Lakes Fish Monitoring Program lists over 550 compounds. (See Appendix G, Table 1.) Priorities among these chemicals can be set based on effects.

   c) Highest volume chemical releases from industrial sites

      This component draws on the Toxic Release Inventory, which includes 528 chemicals. Priorities within the compartment would be based on evaluation of effects data.

   d) Commonly occurring chemicals at hazardous waste sites

      ATSDR has published a list of the most commonly occurring chemicals at hazardous waste sites (Johnson and De Rosa, 1995). These pose a potential hazard to the communities in which these sites are located and, to the extent that such sites are located in lower-income areas, the presence of these sites raises profound issues of environmental justice. These sites are distributed broadly across the United States. Priorities within this compartment would be based on evaluation in Environmental Fate and Transport models and assessment of pertinent effects data.

e) Cosmetics, food additives, and related substances within FDA jurisdiction

This compartment includes substances like cosmetics and food additives which are eaten or are intended to be put on the skin of humans. Therefore, exposure is widespread. Priorities for screening within this compartment would be based on evaluation of data on effects, to the extent that such data are readily available.

f) Chemicals to which there is significant occupational exposure

Occupational exposures can be orders of magnitude higher than environmental exposures. This compartment includes workplace chemicals: (1) to which large numbers of workers are exposed, or (2) that are present in large quantities/high concentrations and therefore represent a disproportionately high risk to workers. EPA regulates occupational exposures to pesticides and pesticide products. OSHA regulates approximately 400 chemicals in the workplace; however, the majority of occupational exposures are unregulated. Integrating chemicals identified in this category with effects information will yield a group of chemicals which pose a high risk to worker populations.

g) Chemicals to which there is widespread environmental exposure

An example, because of the potentially large number of people exposed, would be consumer exposure. The EDSTAC believes that chemicals in consumer products for which there is evidence of endocrine-disrupting effects should be given a high priority for screening and testing. In the environmental realm, chemicals for which there is evidence of their presence in environmental media and for which there is evidence of endocrine-disrupting effects should, likewise, be given a high priority for screening and testing.

2. *Examples* of Exposures Only Compartments

a) High-production volume chemicals

A limited number of chemicals would be drawn from this compartment. These chemicals would have very high production or import volumes and would be included unless there were clear reasons to believe that exposures would not be likely (e.g., a chemical is site limited and not stable). This category would identify chemicals with high exposure potential that are unlikely to be selected in an exposure/effects integrated approach because of few or no effects data.

b) Chemicals to which there is widespread or significant environmental, occupational, consumer, or food-related exposure but no effects data:

Evidence of widespread or significant human exposure (in the environment, workplace, consumer products, or food) should be sufficient to put a chemical on

the priority list for screening and testing. The rationale is that the majority of commercial chemicals have not been tested for endocrine disrupting effects, and therefore a proactive approach is needed for chemicals that entail significant human exposure.

3. *Examples* of Effects Only Compartments

a) Results of HTPS

A relatively small number of chemicals is expected in this category. HTPS is designed to increase available knowledge on effects of chemicals, especially for those chemicals about which little is known. The results of HTPS can assist in setting priorities within other compartments, but can also be used on a "stand-alone" basis, as indicated in Section V of this chapter. Alternatively, this compartment could contain any chemicals that have a positive result in the HTPS assays, but are not otherwise identified as a priority under any of the compartments described above. Chemicals in this compartment could be ranked based on HTPS determinations regarding their potency, while acknowledging that HTPS does not address the full range of endocrine disrupting mechanisms.

b) Results of Epidemiology Assessments

Epidemiological analyses may or may not provide useful information about human exposures to chemicals. Epidemiological studies can provide evidence of health effects related to chemicals. The strength of a causal association between exposure and health effects will vary depending on study design and quality. In general, the weight-of-evidence is greatest for a randomized controlled trial and weakest for simple case-reports. Cohort studies, case-control studies, ecological analyses, and simple demographic or temporal analyses of disease fall in between randomized control trials and case-reports, providing decreasing weight-of-evidence for a causal association between exposure and disease.

c) Results of Laboratory and Field Studies

This compartment would include chemicals that were identified by laboratory or field studies as having the potential to cause effects in humans or wildlife. However, these chemicals would have either no or inadequate exposure data.

4. Specially Targeted Compartments

a) Mixtures

People and other living organisms are continually exposed to mixtures. The EDSTAC does not underestimate the difficulty of addressing these mixtures. Nevertheless, initial steps *must* be taken to understand the implications of these exposures. In Section VII, the EDSTAC identified six types of mixtures from which representative samples of mixtures should be selected as a priority for T1S. It is the Committee's belief that its recommendations represent a reasonable and prudent approach.

b) Naturally occurring non-steroidal estrogens (NONEs)

As described in Section VIII, humans and other living organisms are broadly exposed to a wide range of naturally occurring chemicals that affect hormones. These substances are ubiquitous in food. Individuals exposed to them should be made aware of the benefits and hazards that may be associated with their consumption. Based on such information, consumers may be able to voluntarily alter their diets. As indicated in Section VIII, twelve such substances should be addressed in Phase I.

c) Nominations

The EDSTAC recommends EPA establish a process to allow citizens to nominate chemicals for endocrine disruptor screening and testing. The purpose, criteria, and principles that should guide EPA in developing and implementing the recommended process are described in Section IX of this chapter.

F. Numbers of Chemicals Prioritized and Associated Weightings of Compartments

EPA has not provided the EDSTAC with a target for the number of chemicals the Agency believes should go through T1S in either Phase I, subsequent phases, or for the life of the program. The PSWG of the EDSTAC exchanged views about potential targets for the number of chemicals for each phase of the program but did not attempt to reach consensus on this matter in the hopes of using the EDPSD as a tool that could be used to explore alternative scenarios and targets. The PSWG and the EDSTAC had hoped to use the tool to develop precise recommendations on how to structure the compartments (i.e., how many compartments there should be and how many chemicals should be drawn from each compartment). However, because the EDPSD was not completed before the drafting of the EDSTAC's final report, the EDSTAC (and, in particular, the PSWG that conducted this work on the EDSTAC's behalf) was unable to conduct a "reality check" on how the illustrative compartments might work in practice.

In the absence of having a tool that could be used to both ground its recommendations in the most

up-to-date and relevant data available and to test out alternative priority setting scenarios, the EDSTAC was reluctant to develop recommendations on such questions as how many compartments there should be, how many chemicals should be drawn from each compartment, and how many chemicals should be screened and/or tested in each phase of the program. Additional uncertainties that made it difficult to develop such recommendations include unknown results of the validation and standardization process, laboratory capacity to conduct screens and tests, and the feasibility of conducting screens and tests on chemical substances and/or mixtures with certain physical properties (e.g., gases).

Thus, the number of chemicals to be selected for T1S is a major unknown in achieving greater specificity at this time on how the system should work in practice. For example, if only a small number of chemicals can be screened in Phase I, this dramatically reduces the number of chemicals that can be selected from each compartment, and may dictate the selection of a smaller number of compartments. On the other hand, if the number of chemicals to be screened is relatively large, this provides somewhat greater flexibility in selecting chemicals and could alter the weights assigned to different compartments. Factors such as laboratory capacity, private sector testing response, and the universe of eligible chemicals are variables that may be considered in the determination of the number of chemicals to be screened in Phase I.

Whatever number is chosen, it should encompass chemicals most widely found in biological samples, produced at highest volumes, released in greatest amounts, and most likely to be of environmental concern, and several mixtures to which there is widespread exposure. Moreover, should a decision be made to raise the priority for screening of those chemicals that rank highest in multiple compartments, this will provide increased assurance that screening resources are being directed where they can be most helpful. Beyond the chemicals that rise to the top because of their high rankings in multiple compartments, the question of how many chemicals should be selected from each compartment is a heavily value-driven exercise. *For example and for illustrative purposes only*, one could take all or almost all of the chemicals from a compartment (e.g., measured concentrations in tissues and fluids of living organisms) that is deemed highly important relative to other compartments.

For example and for illustrative purposes only, if the number of chemicals chosen is relatively large, chemicals could be prioritized by:

- Selecting 72% from the integrated exposure/effects compartments;
- Selecting 10% from the exposure-only compartment(s);
- Selecting 10% from the effects-only compartment(s); and
- Selecting 8% from the specially targeted compartments.

Conversely, *and again for example and for illustrative purposes only*, if the number of chemicals chosen is relatively small, chemicals could be prioritized by:

- Selecting 60% from the integrated exposure/effects compartments;
- Selecting 15% from the exposure-only compartment(s);

- Selecting 15% from the effects-only compartment(s); and
- Selecting 10% from the specially targeted compartments.

G. Next Steps (Reaching Closure) on Phase I Priorities for Screening and Testing

The EDSTAC believes it has created a strong, logical, transparent basis for setting priorities for T1S. The Committee recommends that the multi-stakeholder group, described in Section X, G, use the EDPSD tool to experiment with the above categories and compartments to determine more finely the numbers of chemicals that emerge for T1S. The experiment can encompass including or excluding different quantitative thresholds for guiding decisions on the larger categories of priority chemicals, including parameters related to environmental fate and transport and parameters related to reported effects data.

H. Recommended Approach to Setting Priorities for Tier 2 Testing During Phase I of the EDSTP

As described in Chapter Three, the EDSTAC is recommending that the owners/producers of chemicals should be permitted to bypass T1S under two alternative scenarios. "Scenario 1" covers chemicals for which two-generation reproductive toxicity studies are either required by statute (i.e., FIFRA), or where such studies have been completed in the past, but in both cases the studies did not include the additional T2T endocrine disruptor endpoints recommended by the EDSTAC. "Scenario 2" covers chemicals where the owner/producer has decided to voluntarily complete T2T without having completed the full T1S battery or any prior two-generation reproductive toxicity testing.

This section focuses primarily on the need to set priorities for food-use pesticides regulated under FQPA, which is a subset of chemicals covered under Scenario 1, during the first phase of implementing the EDSTP. As discussed below, the EDSTAC recommends that priorities for conducting T2T on food-use pesticides should be based on the FIFRA/FQPA re-registration and tolerance reassessment processes.

Priority setting for T2T for chemicals other than food-use pesticides for which two-generation reproductive toxicity tests have been completed in the past but where the chemical is not regulated under FIFRA/FFDCA, as well as chemicals that bypass T1S under Scenario 2, will generally be driven by the same priorities set during the priority setting phase for T1S unless the producer/owner of the chemical wishes to voluntarily expedite testing. In other words, the EDSTAC recommends that a chemical which receives a high priority ranking for T1S should retain that high priority ranking for T2T even when the owner wishes to voluntarily bypass T1S. Food-use pesticides that bypass T1S under Scenario 1 are likely to be the prime candidates for the alternative approaches to completing the information requirements for T2T described in Chapter Five, Section V. It is also assumed that it may be necessary to assess endocrine-mediated endpoints that had not been adequately assessed in past two-generation reproductive toxicity tests on these compounds. The determination of which alternative tests and/or additional endpoints

need to be conducted will be made on a case-specific basis.

The EDSTAC recognizes that it may be necessary to conduct a limited number of assays that are similar, if not identical, to those that would have been conducted during T1S for chemicals which are permitted to bypass the T1S battery. The purpose of conducting these assays as part of T2T is to gain knowledge about specific mechanisms of action necessary to complete the hazard assessment step and/or to determine whether any adverse effects observed in T2T are in fact endocrine-mediated.

The decision to consider pesticides separately for priority setting was based on practical realities associated with scheduling in EPA's Office of Pesticide Programs. These include ongoing re-registration activities, which have been in progress for more than a decade, and new requirements for tolerance reassessment and registration renewal mandated under the Food Quality Protection Act. These represent the primary scheduling priorities in the Pesticides Program for the foreseeable future.

Under the re-registration program mandated in 1988, EPA reviews older pesticides to ensure compliance with current scientific and regulatory policies. Re-registration is intended to update test data requirements and standards for approval which change over time. During re-registration the Agency issues Data Call-Ins (DCIs). The interval between issuance of the DCI and receipt of data is dependent upon the number and the kind of studies requested. Presently, re-registration is being conducted on compounds for which DCIs were issued en masse shortly after passage of the 1988 amendments to FIFRA or on a case-specific basis thereafter. For the most part, these data have been received by the Agency. Data were requested for 436 active ingredients, and Registration Eligibility Decisions (REDs) have been issued for approximately 200 of the 436 pesticide ingredients (John Housenger, U.S. EPA, personal communication). Generally, neither the DCIs nor REDs issued to-date have systematically dealt with endpoints acknowledged to be endocrine-mediated.

In addition to the re-registration process, food-use pesticides represent a category of pesticides for which EPA has already undertaken a hazard-based priority setting exercise. The food-use pesticides are being reviewed with an eye to tightening regulatory treatment in light of new scientific data and statutory requirements. This priority setting exercise was mandated by Congress under Section 408(q)(3) of the FQPA. EPA is required to reassess all existing tolerances for pesticide residues in or on raw and processed foods for both active and inert ingredients by August 2006. EPA is directed to give priority review to pesticides that appear to present risk concerns based on existing data. In reassessing tolerances, EPA must consider:

- aggregate exposure to the pesticide;
- cumulative effects from other substances with a common mode of toxicity;
- whether there is an increased susceptibility to the pesticide for infants and children; and

- whether the pesticide produces an effect in humans similar to an effect produced by a naturally occurring estrogen and other endocrine effects.

The FQPA requires EPA to review, within ten years, all tolerances and exemptions established prior to FQPA's enactment on August 3, 1996. EPA is required to review 33% of applicable tolerances and exemptions by August 1999, 66% by August 2002, and 100% by August 2006. FQPA also required EPA to publish its review schedule within one year of the law's enactment, which EPA did on August 4, 1997 (62 FR 42019-42030). This general schedule developed by EPA for tolerance reassessment, along with re-registration and registration renewal, are the primary driving forces in scheduling regulatory actions for pesticides and their formulations and inert ingredients. With respect to tolerance reassessment, EPA has divided the pesticide reevaluation process into three categories, which will be reviewed in chronological order over ten years:

- Group 1, the highest priority class, includes organophosphate, carbamate, and organochlorine pesticides. It also includes pesticides classified by EPA as probable human carcinogens (Groups B1 and B2 in EPA's carcinogen ranking system), and possible human carcinogens for which EPA has quantified a cancer potency (Group CQ* in EPA's carcinogen ranking system). Group 1 also includes high-hazard inert ingredients and any pesticides that appear to exceed their reference dose (RfD). [Note that RfD is defined as the daily exposure level of a pesticide which, during the entire 70-year human lifetime, appears to be without appreciable risk of non-cancer effects on the basis of all of the facts known at the time. It is expressed in milligrams of the pesticides as it appears in the diet, per kilogram of body weight per day (mg/kg/day).] The exposure must not exceed 100% of the RfD to meet the reasonable-certainty-of-no-harm health-based standard in the FQPA. The inclusion of certain pesticides in Group 1 is also driven by EPA's need to complete their re-registration by 2002, even though their tolerances may not appear to pose the greatest risk to public health. Also in Group 1 are pesticides for which tolerances and exemptions are in the process of being proposed for revocation.
- Group 2 includes possible human carcinogens not included in Group 1. Group 2 also includes remaining pesticides for which re-registration must be completed by 2002, and other pesticides included for other scheduling reasons.
- Group 3 includes biological pesticides, those inert ingredients not identified as high hazard, and selected other pesticides. It should be noted that biopesticides, mainly the pathogenic microorganisms, are probably not amenable to endocrine disruption screening and testing.

At the time of the FQPA's enactment, there were 9,728 tolerances and exemptions for active and formulation inert ingredients subject to the reassessment requirement. According to the EPA, 8,190 of these are tolerances for active ingredients, 712 are exemptions for active ingredients, and 826 are exemptions for inert ingredients (John Housenger, U.S. EPA, personal communication). The total number of all active pesticide ingredients and inerts currently registered by EPA is approximately 3,400 (Penny Fenner-Crisp, U.S. EPA, personal communication). This includes approximately 900 active ingredients and approximately 2,500 inerts. (Some of the inerts are also listed in the TSCA Inventory.) Of these 3,400, 469 active ingredients are scheduled to be

addressed through the tolerance reassessment process. This includes 228 in Group 1 (scheduled for review by August 1999), 93 in Group 2 (scheduled for review by August 2002), and 148 in Group 3 (scheduled for review by August 2006). There are an additional 823 inert ingredient exemptions that will be dealt with as part of Group 3.

There are both advantages and limitations to using the re-registration and tolerance reassessment processes as the basis for setting priorities for endocrine disruption screening and testing:

- Re-registration and tolerance reassessment priorities were not established specifically with endocrine disruption endpoints in mind. On the other hand, registration renewal, which has yet to begin, could take them into consideration. The current database on reproduction and developmental toxicity for most food-use pesticides reflects the application of the 1985 test guidelines. Non-food-use pesticides may or may not have reproductive or complete developmental toxicity data, depending on their specific use patterns.
- The priority setting process for food-use pesticides is driven by human health considerations, so the entire set of non-human, ecosystem-protection concerns of EDSTAC is not explicitly incorporated. However, most of the food-use pesticides with ecological concerns to non-target organisms appear on the Group 1 and Group 2 lists.
- Tolerance reassessment for Group 1 pesticides is likely to be completed prior to the completion of the validation and standardization of all EDSTAC recommended screens and tests.

Even though the tolerance reassessment process may be complete for Group 1 chemicals before the screening and testing program is fully operational, other opportunities will arise during which the human health risk assessments done for the ten-year tolerance reassessment exercise will be revisited. One of those opportunities will be during the fifteen-year registration renewal cycle. Other opportunities may arise sooner than that, for example during the course of periodic modifications to the registration status of a specific active and/or other product ingredient(s). For instance, requests may be submitted for emergency exemptions (Section 18's), new uses, and/or modifications to existing uses. Each of these actions requires an updating of the previous risk assessment. If the pesticide under evaluation has been shown to share a common mechanism of action with other pesticides, the other pesticides will have to be revisited, as well. Also, when test guidelines are updated, the program will assess whether or not additional data might be needed to upgrade the database on all pesticides for which that test guideline is appropriate. (Such an assessment will need to be done soon in light of the recent upgrading of the multigeneration reproductive toxicity and developmental toxicity test guidelines.) In light of these possibilities, the EDSTAC recommends that HTPS data be used, along with other relevant information, to help prioritize whether and, if so, when these pesticides should be subjected to any additional endocrine disruptor testing prior to the next mandated fifteen-year registration renewal cycle.

Notwithstanding these disadvantages, the EDSTAC recommends that the priorities EPA has established for the re-registration and tolerance reassessment processes be used as the basis for the priorities for subjecting food-use pesticides to T2T. When planning for the registration renewal process begins, the FQPA requirement for endocrine disruptor screening and testing should be designated as a criterion for priority setting. EPA's priority scheme for tolerance reassessment and exemption reviews encompasses many pesticides of potential concern for

endocrine disruption. However, it leaves out several hundred non-food-use active and inert ingredients. These will be addressed using the recommended process for setting priorities for T1S as described above.

XII. Compilation of Chapter Four Recommendations

A. Summary and Scope of Effort

The Priority Setting Work Group based its deliberations on the original Conceptual Framework described in Chapter Three. The work of the group revolved around adapting the Conceptual Framework and included the operational elements necessary for sorting and prioritizing chemicals. The core priority setting process that emerged contained several elements:

- the use of all available existing information;
- the development of a relational database to efficiently access and utilize information;
- an initial sorting of the universe of chemicals into categories based on an operationalized Conceptual Framework;
- the development of high throughput pre-screening data and its incorporation into the database;
- the use of the database to summarize empirical data and estimate fate and effect parameters where possible;
- the use of the database to establish criteria for sorting chemicals where appropriate; and
- the use of a compartment-based concept to accommodate subjective weighting where appropriate.

The EDSTAC viewed its role within EPA's broader mandate to protect human health and the environment and the broader testing authorities available to EPA. As such, the EDSTAC did not limit itself solely to requirements of the Food Quality Protection Act and the Safe Drinking Water Act Amendments of 1996. The Committee believes it is important to have priorities driven by scientific considerations and explicit value judgments, rather than by existing regulatory requirements.

B. The Universe of Chemicals and Initial Sorting

1. The EDSTAC recommends that pesticides, commodity chemicals, environmental contaminants, naturally occurring non-steroidal estrogens (e.g., phytoestrogens, mycotoxins), food additives, cosmetics, nutritional supplements, and a set of representative mixtures be prioritized for endocrine disruptor screening and testing.

2. The EDSTAC recommends that scientific considerations be used as the primary basis for prioritizing chemicals for endocrine disruptor screening and testing. Statutory authority to protect human health and the environment is embedded in long-standing federal legislation, as

well as the Food Quality Protection Act and the Safe Drinking Water Act.

3. The EDSTAC recommends that the chemicals under consideration (approximately 87,000 compounds) be sorted into the following four primary categories based on the operationalized Conceptual Framework:

    - Polymers are to be placed on hold (with some exceptions) pending review of their monomers, oligomers, other components, additives, and degradation products (approximately 20,000 to 25,000 compounds).
    - Chemicals to be considered for endocrine disruptor screening (approximately 62,000 compounds) which lack sufficient data to be placed on hold or to proceed to definitive testing or hazard assessment will be subjected to the priority setting process for T1S.
    - Chemicals with sufficient data are to bypass screening and proceed directly to testing or hazard assessment (approximately 500 to 600 compounds).
    - Chemicals with sufficient data are to go to hazard assessment (expected to number approximately 50 to 100 compounds)

C. Polymers

4. With some exceptions, the EDSTAC concluded that, due to molecular weight, polymers are less cause for concern than other classes of chemicals with regard to endocrine disruption. However, there is some concern regarding the intestinal absorption capacity of neonates. Because of the lack of information on polymers produced prior to 1979 (the date of the initial TSCA Inventory), coupled with the low likelihood that polymers themselves are a concern for endocrine disruption, the EDSTAC offers the following recommendations.

    - All new polymers with a number average molecular weight (NAMW) greater than 1,000 daltons and all previously manufactured (or “existing”) polymers (regardless of NAMW) are to be held from priority setting for endocrine disruptor screening and testing pending the outcome of the screening and testing of their monomer, oligomer, and other components.
    - The monomers, oligomers, and other components of polymers, as well as “new” polymers (i.e., those that went into production after 1979) with a NAMW less than 1,000 daltons are to undergo priority setting, screening, and testing as appropriate.
    - Chemicals on the EPA SDWA Contaminant Candidate List (CCL) should be used to identify the potential degradates of polymers which are most likely to present environmental exposure and which should, therefore, be subjected to priority setting, screening, and testing, as appropriate.

- If monomers, oligomers, or other components of a polymer are determined to have endocrine disrupting properties, an exposure assessment should be performed. At this stage, all potential exposure routes for a component would be determined, including the potential for the component to be available from the polymer.
- As the Agency gains experience with endocrine disruptor screening and testing of monomers, oligomers, and "new" polymers (i.e., those that went into production after 1979) with NAMW less than 1,000 daltons, it should apply that experience toward development of an approach to address "existing" polymers (i.e., those that went into production before 1979).

D. Priority Setting Information Categories and Criteria

5. The EDSTAC recommends using existing exposure-related and effects-related data and information to establish criteria for accomplishing initial sorting. The Committee identified the following subcategories of information that could be used as the basis for sorting and priority setting and developed principles regarding their use.

Exposure-Related Information and Criteria

a) Biological sampling data
b) Environmental, occupational, consumer product, and food-related data
c) Environmental releases
d) Production volume
e) Fate and transport data and models

Effects-Related Information and Criteria

a) Toxicological laboratory studies and databases
b) Epidemiological and field studies and databases
c) Predictive biological activity or effects models (e.g., SARs, QSARs)
d) Results of high throughput pre-screening

E. High Throughput Pre-Screening

6. The EDSTAC found there was a general lack of endocrine effects data for the vast majority of chemicals. To address this problem, the EDSTAC recommends that, if demonstrated to be feasible, eight *in vitro* transcriptional activation assays should be conducted in a high throughput pre-screening mode (i.e., with the use of robotics and other automated processes). The objectives for conducting these assays in a high throughput mode is to:

- provide some information about the affinity of chemicals to bind to the estrogen,

androgen, and/or thyroid hormone receptors;
- use this information in conjunction with other exposure- and effects-related information to determine the priority by which chemicals should be advanced to T1S;
- improve QSAR models;
- provide a source of information to help focus the selection of Tier 2 tests for those chemicals that bypass T1S; and
- generate data that can be used to identify chemicals that may be of concern at low doses.

7. The EDSTAC recommends that the high throughput pre-screening (HTPS) transcriptional activation assays be conducted on:

   - the estimated 15,000 chemicals that are currently produced in an amount equal to or greater than 10,000 pounds per year;
   - chemicals that are permitted to bypass T1S and go directly to T2T;
   - chemicals that are permitted to bypass both T1S and T2T and go directly to hazard assessment; and
   - all pesticides (both active ingredients and formulation inerts).

8. The EDSTAC recommends that HTPS results for the "bypass" chemicals not be used to set priorities for T1S, but to improve QSARs and inform dosing considerations, particularly during the interim period when research on low dose is being conducted, and to inform decisions regarding the types of tests that would need to be conducted in T2T.

9. The EDSTAC recommends that existing QSAR models be derived and supplemented with data from the HTPS assays, thereby expanding the predictive ability of these models.

10. The EDSTAC recommends that EPA explore the feasibility of creating an archive of a subset of HTPS project chemicals which can be accessed by researchers interested in studying endocrine mediated toxicity or in validating new screens for endocrine disruptors.

F. Mixtures

11. The EDSTAC recommends that EPA include a limited set of mixtures that span a range of physical and chemical properties in both the feasibility demonstration project for the HTPS assays, as well as the validation effort for the T1S assays.

12. If the screens are shown to be capable of handling a diverse set of mixtures in the HTPS feasibility demonstration project and the T1S validation steps, EPA should use expert judgment, guided by a set of prioritization criteria, to evaluate the literature and to decide on a limited set of mixtures to enter HTPS.

13. The battery of screens validated for use in the screening program should be used to evaluate the mixtures examined in HTPS. If appropriate, screening should be followed by testing.

14. The EDSTAC recommends that a comprehensive literature evaluation be undertaken to identify exposure and effects data on mixtures that do not undergo HTPS. This information would be used to inform the prioritization for Phase II and subsequent phases of the screening and testing program which would use the same prioritization criteria as those used for single chemicals.

15. The EDSTAC recommends that representative sample mixtures be selected from the following categories and be subjected to HTPS (if feasible) and to T1S:

    - contaminants in human breast milk;
    - phytoestrogens in soy-based infant formulas;
    - mixtures of chemicals most commonly found at hazardous waste sites;
    - pesticide/Fertilizer mixtures;
    - disinfection byproducts; and
    - gasoline.

G. Naturally Occurring Non-Steroidal Estrogens (NONEs)

16. Naturally occurring non-steroidal estrogens include natural products derived by plants (phytoestrogens) and fungi (mycotoxins). Due to the ubiquitous presence of these compounds in foods, and due to the potential additive and antagonist effects of NONEs with other endogenous and exogenous hormonally active chemical substances, the EDSTAC recommends that:

    - NONEs be included in the endocrine disruptor screening and testing program singly and in complex mixtures; and
    - the following NONEs be screened and, if necessary, tested.

      Representative NONEs:

      - Isoflavones: genistein, daidzein, miroestrol, biochanin A, formononetin, equol
      - Flavones: kaemferol, naringenin
      - Coumestans: coumesterol
      - Dihydrochalcones: phoretin
      - Triterpenes: betulafolienetriol (ginseng)
      - Lignans: enterolactone

      Representative estrogenic mycotoxins:

      - Beta-resorcyclic lactones: zearalenone, zearalenol, zearanol

H. Nominations

17. The core priority setting process recommended by the EDSTAC focuses on giving high priority to chemicals with widespread exposure at the national level. The EDSTAC recognizes such a process could result in a low priority for chemicals where exposures are disproportionately experienced by identifiable groups, communities, or ecosystems. Therefore, the EDSTAC recommends that EPA establish a nominations process that:

    - runs parallel to, but is separate and distinct from, the core priority setting process;
    - is designed to allow chemical substances and mixtures for which there may not be widespread exposures on a national scale, but for which there are exposures on a smaller scale, to be eligible to receive a priority for T1S;
    - allows for an early opportunity to submit nominations during each phase of the Endocrine Disruptor Screening and Testing Program; and
    - draws no less than 5% of the total number of chemical substances or mixtures subjected to T1S from substances receiving nominations but not selected through the main priority setting process.

18. The EDSTAC recommends that any nominated chemical substances and/or mixtures that becomes a priority for T1S through the core priority setting process be removed from consideration within the list of nominated chemicals in order to ensure that the priorities drawn from the nominations process will compete only against other nominated chemicals.

19. In keeping with the overall purpose of the nominations process, the EDSTAC recommends that a different set of exposure-related criteria be used to evaluate the priority for nominated chemicals compared to the exposure-related criteria that will be used for the core priority setting process. Specifically, the nominations process should focus on exposures that are disproportionately experienced by identifiable groups, communities, or ecosystems rather than focusing on chemicals for which there is widespread exposure in the aggregate.

20. The EDSTAC recommends that if there are effects data for the nominated chemical, or if the chemical is similar to another chemical substance or mixture for which effects data are available, EPA should utilize those data as a secondary source of information to help set priorities among nominees.

21. The EDSTAC recommends that when the relative priorities of nominated chemical substances or mixtures are evaluated, EPA should consider those that meet the following criteria to be a higher priority than those that do not:

    - chemical substances or mixtures where there is a likelihood of regular exposure, in contrast to those for which exposure occurs only rarely or occasionally;

- chemical substances or mixtures that affect a high proportion of people within a given community or workplace; and
- chemical substances or mixtures for which there may be empirical or estimated (i.e., model derived) effects-related data regarding endocrine disrupting potential.

22. The EDSTAC recommends that EPA make use of all available information when evaluating nominations, including anecdotes, and other information gathered as part of the core priority setting process (e.g., information contained within the Endocrine Disruptor Priority Setting Database).

23. To assist EPA in evaluating nominated chemicals, the EDSTAC recommends that EPA request the following types of information from the public regarding nominations:

- how exposure to the nominated chemical substances or mixtures may be disproportionately experienced by identifiable groups, communities, or ecosystems;
- the reasons for the nomination (which may include both exposure- and effects-related concerns) and any information that provides a basis for those concerns; and
- the degree of support for the nomination from the potentially affected communities and/or workplaces.

I. Endocrine Disruptor Priority Setting Database (EDPSD)

24. The EDSTAC identified and evaluated numerous data sources associated with the exposure and effects information categories and criteria (Appendix G). The Committee endorsed the integration of relevant and useful data sources into a prototype relational database, referred to as the Endocrine Disruptor Priority Setting Database. Although promising, the EDPSD could not be completed within the EDSTAC's time and resource constraints. Consequently, EDSTAC made a number of recommendations regarding continued development and use of the EDPSD.

- EPA should continue to develop and maintain the EDPSD as a tool that can be used to expeditiously sort and prioritize chemicals for endocrine disruption screening and testing.
- The process used by EPA in developing the EDPSD, as well as the process by which it is used, should be open and transparent.
- EPA should convene a multi-stakeholder group prior to the completion of the EDPSD tool to ensure effectiveness, openness, and transparency.
- After completion of the HTPS assays, this group should make use of the tool, along with the "compartment-based" approach to priority setting described below, in assisting EPA as it develops the final priorities for T1S.
- The EDPSD should not be limited to effects data that can be easily placed into a database format, but should also include data from peer reviewed literature.

- EPA should update the EDPSD at least every six months, and more frequently if time and resources permit.

25. The EDSTAC recommends that EPA provide resources to complete the Quality Assurance/Quality Control investigations of files that are currently in the EDPSD. The EDSTAC further recommends that EPA provide resources to add new files to the EDPSD in stages. These files and stages for their addition could include:

1st stage: EPA's and others' databases that provide data on use for industrial chemicals and pesticides; information from pesticide ecotoxicity, fate, and toxicity one-liners; chemicals that are non-food-use pesticide active ingredients and non-food-use other pesticide ingredients; chemicals on the Generally Regarded As Safe (GRAS) list; and chemicals in the FDA Priority Assessment of Food Additives (PAFA) database.

2nd stage: Data on chemical use that were not readily available in databases; chemicals and concentrations of chemicals in National Health and Nutrition Examination Survey (NHANES), Total Exposure Assessment Methodology (TEAM), and Agency for Toxic Substances Disease Registry's (ATSDR) Hazardous Substances Emergency Events Surveillance (HSEES) files; measured chemical fate data; and additional QSARs for endocrine disruptors.

3rd stage: Inclusion of HTPS data and improved QSARs.

The EDSTAC recognizes that the time and resources required to add new files will depend upon a number of factors, including: when pending files are received, the format of received files, the determination of whether to use files as sources of numerical or logical data, conversion of logical files to numerical files, completion of QA/QC investigations of the files and data, and expediency of the input process.

J. Recommended Approach to Priority Setting

26. The EDSTAC identified a number of obstacles to the development of an "ideal" priority setting system, including the uneven quality and quantity of both exposure- and, even more so, effects-related data sources. Major characteristics of this unevenness include:

- Many more data are available on the effects of the relatively small number of currently registered active ingredients in pesticides (approximately 900) than on the thousands of industrial chemicals produced in much larger quantities.
- Biological monitoring data for humans are scarce. A relatively small number of chemicals (on the order of 100 or less) have been routinely sampled in human blood and

urine in the United States, and the major U.S. national program for sampling concentrations in human tissues was discontinued in 1990.
- Monitoring data for other organisms, while more numerous than human data, still focus on a relatively small number of chemicals.
- Data on routine chemical releases to the environment, while markedly better than they were prior to the creation of the Toxic Release Inventory about 10 years ago, still encompass only 528 industrial chemicals and pesticides and frequently rely on engineering estimates rather than actual releases.

27. The EDSTAC recommended several principles to guide the development of a strategy for setting priorities for the large number of chemicals for which there are insufficient data to go to T2T or hazard assessment. The selected system should be transparent, should make use of the guiding principles for exposure- and effects-related data sources, and should be driven by empirical data, but not be held captive by them.

28. The EDSTAC recommends a "compartment-based priority setting strategy" for prioritizing chemicals for T1S.

- The strategy builds upon the identification and evaluation of the different exposure- and effects-related information categories and criteria.
- The term "compartment" refers to the consideration of these information categories either singly or in combination.
- Illustrative examples of the four different categories of compartments include:
  - the integration of exposure and effects information;
  - the consideration of exposure information;
  - the consideration of effects information; and
  - specially targeted priorities (mixtures, nominations, and naturally occurring non-steroidal estrogens).

The specific compartments and the weights and/or order in which they should be utilized have not yet been agreed upon. A target number of chemicals to go through T1S in the first phase of the program or during the life of the program has not been determined. Possible targets and how these targets might be affected by the compartmentalized approach to priority setting have not been agreed upon.

29. The EDSTAC recommends a number of next steps to further develop and refine the compartment-based approach to priority setting, including:

- use of the EDPSD by a multi-stakeholder group to further characterize and define what will be contained in each compartment;
- whether, and if so, how to prioritize the compartments; and
- how to address the possibility of overlaps between compartments.

30. The EDSTAC recommends using the schedule EPA has established for tolerance reassessments and pesticide re-registration under the FQPA for setting priorities for those food-use pesticides that meet the criteria for bypassing T1S and going directly to T2T. When planning for the registration renewal process begins, the FQPA requirement for endocrine disruptor screening and testing should be designated as a criterion for priority setting.

31. The EDSTAC recommends that priorities for T2T for all other chemicals (i.e., non-food-use pesticides and other chemicals where the owner either wishes to voluntarily bypass T1S, or where the owner has met the criteria for completing the alternative, functionally equivalent, T1S assays) should be established on a case-specific basis. However, the EDSTAC recommends that chemicals which receive a high priority ranking for T1S should retain that high priority ranking for T2T, even when the owner wishes to voluntarily bypass T1S.

XIII. Literature Cited

Ankley, G., S. Bradbury, J. Hermens, O. Mekenyan, and K.E. Tollefsen, "Current Approaches to the Use of Structure Activity Relationships (SARs) in Identifying the Hazards of Endocrine Modulating Chemicals to Wildlife," in Tattersfield, L., P. Matthiessen, P. Campbell, N. Grandy, and R. Länge (Eds.), 19-40 SETAC-Europe/OECD/EC Expert Workshop on Endocrine Modulators and Wildlife: Assesment and Testing, SETAC-Europe, Brussels, 126, 1997.

Adams, N.R., "Phytoestrogens: Lessons from Their Effects on Animals," Proceedings of the Nutrition Society of Australia, 1996.

Baintner, K., "Intestinal Absorption of Macromolecules and Immune Transmission from Mother to Young," CRC Press, 1986.

Cassidy, A., "Physiological Effects of Phytoestrogens in Relation to Cancer and Other Human Health Risks," *Proceedings of the Nutrition Society*, 55, 1996, pp. 399-417.

Clarke, R. et al., "Estrogens, Phytoestrogens and Breast Cancer," *Advances in Experimental Medicine and Biology*, 40, 1996, pp. 63-85.

Cowan, C.E., D. Mackay, T.C.J. Feitel, D. van de Mount, A. DiGuardio, J. Davies, and N. Mackay, "*The Multi-Media Fate Model*," 1995, pp. 78.

Gavaler, J.S., E.R. Rosenblum, and S.R. Deal, "Hidden Hormones in Alcoholic Beverages," R.R. Watson (Ed.) Drug and Alcohol Abuse Reviews, *6*, Alcohol and Hormones, Humana Press Inc., Totowa, N.J., 1995.

Heindel, Jerrold J. et al., "Assessment of the Reproductive and Developmental Toxicity of Pesticide/Fertilizer Mixtures Based on Confirmed Pesticide Contamination in California and Iowa Groundwater," *Environmental and Applied Toxicology*, 22, 1994, pp. 605-621.

Jensen, A.A., and S.A. Slorach, (Eds.), "Chemical Contaminants in Breast Milk," Boca Raton, FL, CRC Press, 1990.

Johnson, B.L., and C.T. De Rosa, "Chemical Mixtures Released from Hazardous Waste Sites: Implications for Health Risk Assessment," Toxicology 105, 1995, pp. 145-156.

Kleinman, R.E., and W.A. Walker, "Antigen processing and uptake from the intestinal tract,"

Clin. Rev. Allergy, 2(1), 1984, pp. 25-37.

Lecce, J.G., and C.W. Broughton, "Cessation of uptake of macromolecules by neonatal guinea pig, hamster and rabbit intestinal epithelium (closure) and transport into blood," *J. Nutr*. 103(5), 1973, pp. 744-750.

Lien, L.L., and E.J. Lien, "Hormone Therapy and Phytoestrogens," *Journal of Clinical Pharmacy and Therapeutics*, 21, 1996, pp. 101 - 111.

Markovits, J., "Inhibitory Effects Of The Tyrosine Kinase Inhibitor Genistein on Mammalian DNA Topoisomerase II," *Cancer Research*, 49, 1989, pp. 5111-5117.

Richard, S.E., and L.U. Thompson, "Phytoestrogens and Lignans: Effect on Reproduction and Chronic Disease," *Antinutrients and Phytochemicals in Food*, American Chemical Society, Chapter 16, 1997, pp. 273-293.

Safe, S.H., and K. Gaido, "Estrogens and Anthropogenic Estrogenic Compounds," *Environmental Toxicology and Chemistry*, 17, 1998, pp.119 -126.

Sheehan, D.M., and K. Medlock, "Current Issues Regarding Phytoestrogens," *Polyphenols Actualites.*, 13, 1995, pp.22-23.

Swanson, M.B., and A.G. Socha, "Chemical Ranking and Scoring: Guidelines for Relative Assessments of Chemicals," SETAC Press, Pensacola, FL, 1997, pp. 186.

Thomas, J., "Phytoestrogens and Hormonal Modulation: A Mini-Review," *Environmental Interactions*, 1, 1997, pp. 5-12.

U.S. EPA, Guidelines for Developmental Toxicity Risk Assessment, Fed. Reg. 56: 63798-63826A, 1991.

U.S. EPA, Reproductive Toxicity Risk Assessment Guidelines, Fed. Reg. 61: 56273-56322, 1996.

U.S. EPA, Guidelines for Neurotoxicity Risk Assessment, Fed. Reg. 63: 41845, 1998.

Verdeal, K., and D.S. Ryan, "Naturally Occurring Estrogens in Plant Foodstuffs – A Review," *Journal of Food Protection*, 42, 1979, pp.577-583.

Walker, W. A., "Antigen Handling By the Gut," *Arch Dis Child*, 53(7), 1978, pp.527-531.

Weaver, L.T., M.F. Laker, et al., "Milk Feeding Changes in Intestinal Permeability and Morphology in the Newborn," *Journal of Pediatr Gastroenterol Nutr.*, 6(3), 1987, pp. 351-358.

Weise, T., and W.R. Kelce, "An Introduction to Environmental Estrogens," *Chemistry and Industry*, 1997, pp. 648-653.

Westrom, B., J. Svendsen, and C. Tagesson, "Intestinal permeability to polyethyleneglycol 600 in relation to macromolecular "closure" in the neonatal pig," *Gut.*, 25, 1984, pp. 520-525.

Westrom, B.R., C. Tagesson, et al., "Decrease In Intestinal Permeability to Polyethylene Glycol 1000 During Development in the Pig," *J Dev Physiol.*, 11(2), 1989, pp. 83-87.

Wiseman, H., "Role of Dietary Phyto-Oestrogen in the Protections Against Cancer and Heart Disease," Bioactive Components of Food, 658th Meeting of the Biochemical Society, Liverpool England (UK) April 16-19, 1996 Biochemical Society Transactions 24 (3), 1996, pp. 795-800.